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THE APPROACH TO THERAPEUTICS THROUGH THE MODE OF ACTION OF DRUGS ON CELLS.

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A STRIKING feature of most reports in pharmacological journals is the almost totally empirical approach of the investigations to the problems considered. This is especially so when a new compound is undergoing its pharmacological "trials". Occasionally with substances closely related to some well-known substance, some slight predictions about certain qualitative aspects may be made, but from a quantitative point of view it is not even possible to speculate as to the result. The most fertile field of pharmacology is therefore that in which are found basic generalizations on the manner of action of drugs on cells. Only two things are involved in a study of pharmacology: a chemical substance and a cell. The physico-chemical properties of the substance have usually been investigated thoroughly. One should then investigate the mode of action of drugs on the cells. We know of many drugs which raise or lower blood pressure, we know of other drugs which have an antagonistic or synergic action when used with these drugs, but we know nothing of the mechanism by which the cells surrounding the arterioles and veins are activated. Consequently it is not surprising that we are unable to treat derangements of the blood pressure, such as hypertension or shock. It is for this reason that all work undertaken over the last few years has been concerned more with determining how the actions of various drugs are brought about than just a recording of the action of this or that compound. No claim for novelty is made. The first serious attempt to account for the action of drugs was that made independently by Myer and Overton at the turn of the century. It is not proposed to review in detail the various theories which have been propounded. The older hypotheses, with their modern interpretations, have been reviewed by Henderson.⁽¹⁾ The following summaries will serve to illuminate the aspects to be discussed below.

The Myer-Overton theory is in reality an observation that of the anæsthetics known at that time, the higher the partition coefficient ($\frac{\text{oil}}{\text{water}}$) the better the action. Apart

from the usual objections that the partition in the body is really a lipoid/lymph one and that new anæsthetics do not fall in with the scheme, there is the final criticism that the theory goes no further than saying that the membrane is affected, but does not explain how this loss of function is brought about. The same may be said of Traube's adsorption theory; it is merely an observation that substances which lower surface tension of water pass more easily through cell membranes. It is contended that all these theories suffer from one cardinal defect. They are far too general in their applications. The various protagonists have taken as their basis the "common cell", which is no more an entity than the "average man". The fact that during evolution the cell has undergone changes leading to specialization has been neglected. Verworn maintains that deprivation of the cell of oxygen accounts for anæsthesia, but this neglects consideration of the level in the central nervous system at which the anæsthetic acts, for surely the structure and therefore the metabolism of cells will vary in different positions in the brain. The same objection of differences in cellular structure must weigh heavily against the all-embracing idea that drugs act by interfering with colloid structures (Claude Bernard and Bancroft). An anæsthetic may depress many cells, but it does not follow that the mechanism on the different cells is the same in each case.

One point which most theories of drug action share is that they choose to consider ways in which a chemical may depress a cell. Have the older (and some modern) pharmacologists unconsciously tackled the easier rather than the difficult task, that is, to consider depression before stimulation? It is indeed simple to say: "Deprive a cell of oxygen and it will cease to function"; but the opposite does not hold. It has never been shown that excess of oxygen will bring about activation of a cell, as for instance that adrenaline will bring about contraction of a smooth muscle cell.

In 1943 a discussion was held at the Faraday Society on the modes of drug action.⁴⁰ The discussion was between the leading pharmacologists, chemists and physicists of the day; from their deliberations only two points emerge. The first, a warning by Sir Henry Dale that our approach in the past has been to a certain extent illogical; this idea is put so succinctly by him that I shall take the liberty later of quoting in full. The second I do not think has been stressed by any one author; it is that no general consideration of drug action is possible. We must consider our problem as a unit. Each unit must be investigated as a specific case because it contains features absent from other cases. Christophers deals with the inhibitory action of drugs on the respiration of malarial plasmodia. Lourie has studied human trypanosomiasis, a disease of essentially two stages. In the first the infestation is practically limited to the blood and lymphatic system. After a variable time, during which the tissue spaces of the various organs may or may not be invaded, there follows the second and very serious stage in which some of the trypanosomes have found their way into the brain. A drug intended as a remedy for sleeping sickness has therefore a considerably more exacting task to perform in the second than in the first stage of the disease, for the reason that those parasites which have penetrated beyond the blood stream into intimate relationship with the brain cells are relatively sheltered from full blood concentration of the trypanocidal agents. This has led to a revival of the physiological concept—the blood-brain barrier. There are, of course, anatomical and physiological difficulties in exact localization, but that it exists pharmacologically there is no doubt. When, however, one comes to consider the factors which determine the ability of compounds to penetrate the blood-brain barrier, the subject becomes somewhat confused. With non-polar substances lipid solubility or surface activity plays an important part. Among polar substances, molecular size, lipid solubility and diffusibility are of minor consequence, the important factors being the electrochemical properties of the substances concerned. Here again, after breaking new ground, we find the investigators treading the old path of generalization to which Dale has referred. Perhaps it would be better, having introduced the new concept of blood-brain barrier, to investigate this thoroughly rather than to assume it is composed of "common cells" which permit the passage of drugs in response to some general physico-chemical rule.

Quastel, taking the old idea of Verworn that narcotics act by deprivation of oxygen, has made a creditable attempt to be specific. He has employed the inhibition of oxygen uptake by brain slices as an index of narcotic activity. He finds with the barbiturates a pretty parallelism. He has extended this to narcotics of different chemical types. This has been followed by an investigation of the combustion of the various intermediates of carbohydrate metabolism. Oxidations of glucose, lactate and pyruvate are most affected, whilst succinate and p-phenylenediamine are undisturbed. Once again Quastel tried to generalize. It had long been known that narcotics inhibit dehydrogenases and it seemed a simple explanation of narcotic inhibition of brain respiration to suppose that the effect was due to inhibition of dehydrogenases, affecting glucose, lactate or pyruvate. The results showed that this was not the case. More recent work has restricted the action to possibly the flavoprotein component of a respiratory system.

A modern version of Ehrlich's general theory of drug action was put forward and critically examined by A. J. Clark. It is assumed that drug molecules combine with specific receptor substances, which in most cases appear to be situated on cell surfaces; the physiological action of the drug is regarded as occurring subsequently to, but in consequence of, this drug-receptor combination. The nature of the drug-receptor combination is unknown, but as it is often reversible, it is regarded as analogous to the enzyme-substrate combination assumed to precede enzyme activity. To Clark must go the credit for being one of the foremost in introducing quantitative method to problems of drug action. Intimately bound up with Clark's theory is the relationship between chemical structure of the drug and its pharmacological properties. It is from this aspect that Ing deals with the problem; he gives examples of how it has been possible to predict

satisfactorily the behaviour of new compounds. However, the whole paper is marked by a note of caution. Whilst it is possible sometimes to predict action from structure, this is not always so, and certainly changes in intensity of action resulting from even the most trivial alterations in structure cannot be predicted. More difficult still of interpretation is the fact that drugs of diverse structure may have similar pharmacological action, or drugs of similar structure may have diverse pharmacological action. Sometimes the first may be explained by the fact that different sites of action are involved; for instance, acetylcholine and eserine are both parasympathomimetic, but one acts directly on the cell, the other on an enzyme. This will not serve as an explanation of the similar action of such diverse substances as acetylcholine, muscarine and pilocarpine. Once again we are forced back to the cell as the key to the problem.

The final paragraph of this paper shows how true this is:

It has been tacitly assumed throughout this article that all the receptors in a given tissue are equally accessible to drugs and equally effective in a physiological sense. Both assumptions are rather improbable; it is more likely that the receptors are subject to individual variation.

To those authors in this series who sought to explain drug action by purely physico-chemical considerations, such as partition coefficients, surface activities, dissociation constants *et cetera*, one can do no better than to quote at length from Dale's introductory address, of which previous mention has been made (page —):

I suspect that we have tried to attribute to such parallels between physico-chemical properties and pharmacological action, as we can observe in homologous series, a significance beyond that which they can properly bear. Significance, of course, these parallels have; since any kind of vital process is dependent on change in complete physico-chemical systems, the intensity of a particular action upon it, observed in an homologous series as likely to be conditioned by some physical chemical property that waxes and wanes again as we ascend the series; and we seem to have several such properties to choose from, with maxima at the same member of the series. The point which I wish to emphasize, however, is that this coincidence of maximum activity with a maximum of oil solubility or of activity on interfacial tension at a particular type of surface may not throw any light at all on the specific appearance in that series of the physiological activity which we are studying and which may be a highly specialized and extremely complicated one. A good example occurs in the papers to be presented by Dr. Ing and Dr. Schulman, both of whom happen to cite the interesting maximum of oestrogenic activity at the di-ethyl substitution stage in the series of dihydroxy-stilbenes. Dr. Ing is interested in this maximum from the point of view of structural chemistry and Dr. Schulman in its coincidence with the form most actively adsorbed on a protein surface. Now I am certainly not suggesting that this coincidence is not of interest, but I do venture to urge that we should not allow ourselves to assume that it even begins to account for the occurrence of the highly specific and complex activity which we call oestrogenic. It does not tell us what initiates the complicated train of events in the mucous membrane of the female genital tracts which constitutes what we call oestrus. That surely is not a general property of substances which are powerfully adsorbed on protein interfaces.

Dr. Ing alludes to the remarkable specificities of certain chemicals for physiologically effector cells—nerve, muscle and gland cells—and the association of these with innervation by different parts of the autonomic nervous system—surely one of the most fascinating of pharmacological mysteries, and one which remains a mystery even with our present knowledge of the physiological interaction of adrenaline and acetylcholine in the transmission of different nervous effects. It is a mere statement of fact to say that the action of adrenaline picks out certain effector cells and leaves others unaffected; it is a simple deduction that the affected cells have a special affinity of some kind for adrenaline; but I doubt whether the attribution to such cells of "adrenaline receptors" does more than restate this deduction in another form.

If the review of Albert⁽⁴⁵⁾ is read closely, it is evident that the author, while strongly supporting the hypothesis of Stearn that increasing basicity favours bacteriostatic activity with evidence from the amino-acridine series, suggests that the picture is not complete. If maximum activity in one chemical series coincides with a definite value of some physico-chemical constant whilst another series possessing the same constant is without activity, then the first series must possess in addition another unknown factor absent from the second series. Perhaps the coincidence of several factors is required—an event which, according to the laws of probability, would happen only with very few series.

To summarize again the lessons learnt so far, it should be said that one must not generalize and one must return to a study of the action on, and the response of, a particular cell to a definite chemical or group thereof.

It is in this light that the following results are presented.

The opening example is the confirmation of a prediction which was made during some work on the mode of action of barbiturates. Gruber *et alii*⁽⁴⁶⁾ had shown that barbiturates affected the transmission of impulses at the end of the post-ganglionic fibres of the cardiac vagus nerves. Shaw⁽⁴⁷⁾ extended this work to the post-ganglionic fibres of the intestine, and later Keogh and Shaw showed that transmission at voluntary nerve endings was also affected. (See Figure 1.) Trethewie⁽⁴⁸⁾ has demonstrated interference with humoral transmission. It was thus apparent that

collapse after the intravenous administration of quinine in cerebral malaria.

Brodie and Dixon⁽⁴⁹⁾ were the first to report that small doses of adrenaline may cause a fall in blood pressure, whilst larger doses will produce a rise. The explanation offered is, according to Cannon and Lyman,⁽⁵⁰⁾ that the action is due to direct dilator action on constricted arterial muscle, that is, the one key (adrenaline) can both lock (contract) and unlock (relax) the same cell. Dale (1913) does not agree with this but maintains that there are two types of cells, those which contract to adrenaline (predominant) and those which are relaxed, of which only a few are present. Hartman⁽⁵¹⁾ supports this.

Another aspect of adrenaline's vaso-depressor activity is the phenomenon of "vaso-motor reversal" (Dale⁽⁵²⁾). That is to say, a dose of adrenaline which will produce a rise in blood pressure will after ergotamine produce a fall. The usual explanation is that ergotamine paralyzes the contractor cells, but not the minority depressor cells, whose action is now unmasked.

Hutchinson, Shaw and Wragge,⁽⁵³⁾ whilst investigating the vasomotor reversal brought about by yohimbine, were both puzzled and annoyed to find that one cat in three responded to all doses of adrenaline with a fall in blood pressure. Since this time this ratio has been maintained and has been investigated as time permitted. It is independent of the anaesthetic or mode of preparation of the animal; that is to say, it has been obtained with ether,

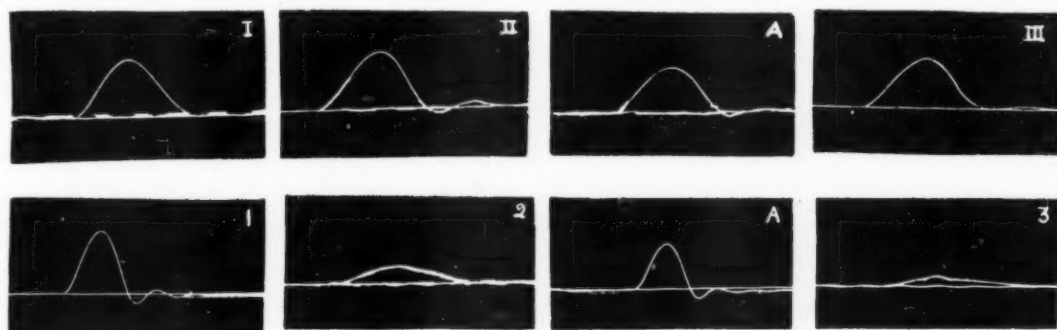


FIGURE 1.

Frog gastrocnemius preparation. Top row: control preparation untreated. I, II, III = nerve stimulated at 0, 120 and 150 minutes respectively; A = muscle only stimulated at 120 minutes. Bottom row: preparation treated with second 1 in 1,000. 1, 2, 3 = nerve stimulated at 0, 120 and 150 minutes respectively; A = muscle only stimulated at 120 minutes. When the nerve only was treated the response was unaffected 150 minutes later.

barbiturates had an action at nerve endings rather than on nerve fibres or muscle cells. It would therefore be of interest to see if this rule held for sensory nerve endings. That is to say that one of the commonest drugs in medicine might possess the hitherto unsuspected property of inducing local anaesthesia. This was tested by means of the intradermal weal method and a 5% solution of either "Luminal", "Nembutal" or "Amytal" was found to compare favourably with a 2% solution of procaine.

The major problem with which we have been concerned in the last five years has been the action of adrenaline on the vascular system as exhibited by alterations in blood pressure of the cat on intravenous administration.

If the subject is examined historically, one notices a definite though almost unstated change from the early rigid conception of adrenaline as purely pressor, as paper followed paper showing that certain vascular areas responded to adrenaline by dilatation. In spite of all this later work, adrenaline (or some derivative) is still regarded, at least by clinicians, as the pressor substance *par excellence*. Our experience with over 200 animal experiments does not enable us to share this view, and it is thought that the subject of sympathomimetic effects in medicine should be reviewed. It is interesting to note in this connexion that in the condition of traumatic shock the classical ideas of adrenaline are undergoing revision. We shall refer again later to the action of adrenaline following

"Nembutal", chloroform or decerebrate and decapitate preparations. However, the frequency with which the phenomenon is exhibited is greatest with ether (which tends to raise the blood pressure) and rare with chloroform (which depresses the blood pressure). Similarly, it is not often seen in the decapitate preparation, but it has been observed and is not therefore of entirely central origin. From this it may be concluded that the response of an animal to adrenaline is not so much a function of the drug as a result of the environment of the cell at any one moment, that is, whether the pressure is high or low.

To explain the action of adrenaline in these anomalous cats is difficult. It is not that the individual cat behaves atypically. For a cat which at the commencement of an experiment may respond with a fall to all doses of adrenaline, may later on, especially if chloroform is administered, respond with a rise. More rarely the opposite may happen. Two explanations are possible. All smooth muscle cells lining the vessels are identical and may, according to the pressure on them, contract or relax in response to the same drug. This seems incredible and is certainly impossible on the cell receptor theory of Clark. The alternative is that there are two types of cells present, one contractile to adrenaline, the other relaxing. In this case, when the blood pressure is high, we can imagine all the contractile cells in a state of maximum tension and unable to contract further; therefore if now adrenaline is

administered, the only cells capable of responding are those giving a depressor response.

The fact that certain cats respond normally to adrenaline raises an interesting problem. Cannon, by his emergency theory that the function of adrenaline is to fit the animal for "fight or flight", has considered that an elevation of blood pressure is beneficial to all animals. Is it possible that a fall is regarded as more necessary by some?

A study of the vasomotor reversal phenomenon was next made. That produced by ergotoxine was discovered by Dale.⁶⁰ It is, however, open to a serious objection in so far as that experimentally it is not produced until the administered ergotoxine has produced a rise in blood pressure, a condition in itself which is likely to lead to a fall in blood pressure on injection of adrenaline, as we have already shown above. This objection does not apply to that reversal produced by yohimbine, first studied by Raymond Hamet⁶¹ and later by Hutchinson, Shaw and Wragge,⁶² or by quinine and alstonia (Keogh and Shaw⁶³), for in these cases the drug produces a transient fall in blood pressure and the second dose of adrenaline is not administered until the pressure has returned to normal. The production of the vasomotor reversal by quinine is not as consistent as that produced by yohimbine. Out of some fifteen experiments only about five gave a definite reversal, but in the remainder the pressor effect was completely abolished and no change in blood pressure resulted on injection of adrenaline. We now have an interesting series of three or four drugs of diverse structure which bring about the same action. The interest is heightened when the response of the blood pressure to calcium is considered with this series.

Keogh and Shaw⁶³ showed that an intravenous dose of calcium chloride which would normally raise the blood pressure would, after administration of quinine, produce a fall in blood pressure. Since publication of this paper the following important parallelism between the action of adrenaline and calcium has come to light.

It has been mentioned earlier that normally about one-third of the cats investigated responded to adrenaline with a fall in blood pressure. It has now been found that those cats which yield a pressor action with adrenaline do so also with calcium, and those which yield a depressor effect exhibit a fall also with calcium (Figure II). But the

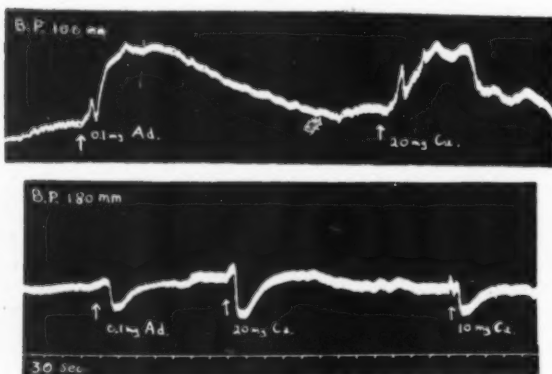


FIGURE II.

Cat, "Nembutal" and ether. Blood pressure. Top tracing: typical pressor response of the blood pressure of a cat to adrenaline and calcium. Bottom tracing: typical depressor response of the blood pressure of a cat to adrenaline and calcium. The tracings illustrate the point that in individual cats the response to adrenaline and calcium is identical.

parallelism does not end here. Those cats which show an abolition or lowering of the blood pressure by adrenaline after yohimbine, quinine or alstonia, provide a similar reversal or abolition with calcium. That the action of calcium is a direct one on the vessels and is not indirectly due to liberation of adrenaline from the adrenals has been shown by repetition of the experiments on adrenalectomized animals. These results all agree with the well-known

sympathomimetic actions of adrenaline and calcium. But, taken in conjunction with the results to follow, they have led to what is thought to be a new conception of drug action, a new weapon with which to attack the problem of the mode of action of drugs on cells. It seems to us that groups of drugs exhibit a pattern of action.

It is proposed now to show the threads of pattern of the actions of adrenaline, calcium, yohimbine and quinine in the body. Most of the work will be found in the papers already mentioned (Keogh and Shaw^{63,64}), but some unpublished data will be added.

If a piece of intestine is suspended in an organ bath and excess calcium is added, the smooth muscle of the intestine relaxes. If the intestine is now treated with quinine, yohimbine, alstonia or strychnine (but not with other alkaloids) a contraction is observed when calcium is added. This is referred to as the "calcium reversal". It is due to the physiological removal of calcium ions from solution by the drugs named because the phenomenon is obtained if the intestine is treated with oxalate, citrate or calcium-free tyrode solution.

The interaction between calcium and quinine and yohimbine is demonstrated in the case of striated muscle by measuring the tension produced on stimulation of the peroneal nerve. If quinine is perfused through the muscle, the tension developed on stimulation of the peroneal nerve increases. This increase is thought to be due to immobilization of the calcium ions because perfusion with citrate oxalate or tartrate (all of which render calcium unionized) yields a similar increase in tension. More recently this "quinine" effect has been obtained with yohimbine (Figure III) and methylene blue (the latter is interesting because it has slight antimalarial activity). A similar beneficial effect of adrenaline on the contraction of voluntary muscle has been demonstrated by Bülbring and Burn,^{65,66} especially in the case of fatigue.

To collect the threads again it is thought that there is a pattern drawn by adrenaline, calcium, quinine and yohimbine when their action is followed on smooth or striated muscle cells. The outline is admittedly shadowy, but two motifs seem to be well defined. The first is that adrenaline and calcium are extraordinarily closely related in their action, suggesting that the action of one is brought about by the release of the other; but in the absence of precise

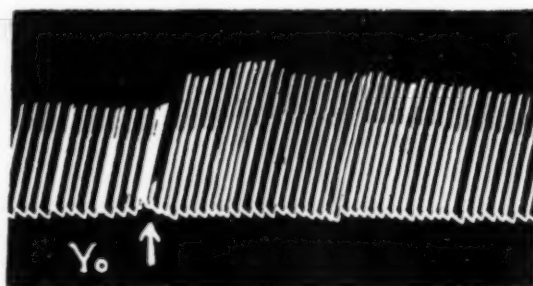


FIGURE III.

Dog. Contractions of *tibialis anticus* on stimulation of peroneal nerve. Note increase in tension on administration of five millilitres of yohimbine 1 in 1,000.

knowledge of the role played by calcium in the cell or its membrane it is not proposed to theorize further. Perhaps the activation of a cell by adrenaline is brought about by changes in permeability due to calcium interchanges as suggested by Heilbrunn. This author suggests that stimulation causes a release of calcium from the cell cortex and this calcium then causes a clotting or gelation of the interior protoplasm; it is possible to suppose that anaesthetics prevent calcium release, or that they prevent that second stage of the reaction, that is to say, the clotting.

But once again it is thought that the dragon of generalization is raising his head. When one compares the parallelisms between adrenaline and calcium and acetylcholine and potassium, one is tempted to formulate the following hypothesis. The simple inorganic ions, calcium

and potassium, were the mediators or hormones in the nervous systems of lowly forms of life, but as the evolutionary scale has ascended Nature has found it necessary to abandon the simple for the complex organic compound, at the same time retaining the propensity of reacting, sometimes imperfectly, to the primæval stimulus.

The second motif is much stronger. It is thought that a perusal of the experimental evidence suggests very strongly that quinine and yohimbine act on cells by reducing the available calcium ion concentration. It is of course realized that this only constitutes one step along the road; it does not explain the mechanism of the action of the calcium.

Summary.

To summarize, it is suggested that a study of the mode of action of drugs on cells is the quickest road to therapeutics, and from the survey just presented certain points of clinical importance arise. The use of barbiturates as possible local or spinal anaesthetics and a statistical investigation of the action of sympathomimetic substances on the human cardio-vascular system together with a study of calcium metabolism in the treatment of malaria with quinine may yield interesting results. The pharmacological similarity of quinine and yohimbine has suggested the use of the latter in malaria, a point which is already under investigation. And finally it has been shown that it is unwise to combat collapse following intravenous injection of quinine by the administration of adrenaline because in the presence of quinine the usual actions of adrenaline are antagonized or even reversed.

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EXPERIENCES, DANGERS AND SEQUELÆ OF SULPHONAMIDE ADMINISTRATION.¹

By R. G. S. HARRIS,
Sydney.

As representative of the Section of Urology at this combined meeting I should like to thank those members of my section who have made case records available to me.

The introduction of the sulphonamide drugs some nine years or so ago commenced an era of chemotherapeutic advances which is still in progress. As various new combinations have entered the field tolerance has been improved and effectiveness has been enhanced. At the same time the dangers of administration have increased and toxic manifestations have become more serious.

In the urinary tract the most alarming complication is the deposition of crystals and the formation of calculi. Whilst this calamity may generally be avoided by the adequate administration of fluids, idiosyncrasy to the sulphonamide drugs occurs not infrequently and caution must always be the watchword.

Apparently three types of renal damage are found: obstructive, focal necrotic and acute nephritic. Obstructive renal damage is due to deposition of crystals of the acetylated drug, which plug the tubules, form calculi in the pelvis and obstruct the ureter. Widespread focal necrotic damage occurs, in which the kidney is only one of many organs involved, but the renal "shut-down" provides the frequently fatal insult. Acute nephritic damage has as its clinically striking features anuria and uræmia, without focal necrosis or crystallization. Hematuria and lumbar, iliac or abdominal pain are the earliest symptoms of impending secretory inhibition, and demand the immediate withdrawal of the drug.

Crystalline deposits from sulphanilamide and sulphapyridine are soluble in alkaline solutions; those of sulphathiazole are considerably less so; whilst sulphadiazine crystals are quite insoluble and depend for their removal on mechanical measures. Of sulphamerazine I have had no experience.

Most organisms affecting the urinary tract respond to sulphadiazine, which I think is the drug of choice; exceptions are *Streptococcus faecalis*, some strains of colon bacilli and *Bacillus proteus*. It is, however, a *sine qua non* that any obstructive urological abnormality must receive appropriate treatment before the goal of urinary sterility can be attained.

It has been my practice to administer alkali—generally "Citralka"—along with the sulphonamide drug. This, by reducing the pH of the urine, enhances the action of the sulphonamide, reduces the incidence of gastric upset, and diminishes the danger of crystallization. Fluids by mouth are forced during the time the drug is being taken, four to five glasses a day being the minimum.

With regard to dosage, it is as a rule unnecessary to "push" the drug in the commoner genito-urinary infections, two to three grammes a day being sufficient. I rarely continue the administration for more than six days without a pause. After four days the tablets are given again for another six days. In fulminating conditions two tablets are given every four hours for twenty-four hours, after which the usual routine is followed. When total renal function is impaired, and for the very old and the very young minimal dosage—namely, half a tablet every four hours—gives most satisfactory results.

Anuria.

When anuria or oliguria has developed several lines of treatment are available. It may be remembered that, after ligation of both ureters, death does not supervene until about the tenth day. It will be seen, therefore, that a fairly safe margin of from six to seven days is available, during which conservative methods may be tried.

The sulphonamide drug must be immediately withdrawn. Administration of alkalis and of copious fluid by mouth is commenced. Occasionally some sharp "kidney punches"

¹ Read at a meeting of the New South Wales Branch of the British Medical Association on April 26, 1945.

may dislodge crystals and relieve colic and impending obstruction. Heat, in the form of "inductothermy" or infra-red rays, or even the use of the shock cradle, is sometimes effective in stimulating renal activity. In the absence of a satisfactory response to these measures intravenous therapy is commenced. The solution should be administered by the slow drip method, at the rate of about thirty drops per minute.

If vomiting has been severe, chlorides must be replaced with normal saline solution and 5% dextrose solution. Later, 10% saline solution and 10% dextrose solution may be introduced as a powerful stimulant to renal secretion. Hyperchloraemia should be avoided and the administration of 5% dextrose solution in distilled water can be continued for some days if desired. The intravenous administration of sodium sulphate solution is also worthy of a trial. In one of my cases of anuria from sulphathiazole crystals there was a prompt response, and this treatment has proved most effective in anuria and oliguria from other causes. The intravenous administration of sodium bicarbonate solution, sodium citrate solution and 1/6 molar sodium lactate solution I have not used, though they have been recommended.

It must always be borne in mind that obstruction by crystals is the most common cause of the anuria—crystals in the tubules, the pelvis or the ureter—and for this reason tentative arrangements for endoscopic manipulation should be made. I think this should be carried out not later than the sixth day; in most cases it can probably be performed earlier with advantage. Ureteric catheterization, preferably bilateral, with lavage of the renal pelvis with warm normal saline solution or warm sodium bicarbonate solution should be carried out. Inlying ureteric catheters should be retained so that lavage can be continued at regular intervals.

It is not always possible to catheterize each ureter, either for mechanical or for anatomical reasons; but, fortunately, relief of the obstruction to one kidney is generally followed by increased activity of the other within a short period of time.

If all these measures fail, the last recourse is to surgical intervention.

Generally that kidney is selected for operation from which the signs and symptoms have been most severe. On exposure the pelvis is opened, the kidney is massaged and lavaged, and bougies are passed down to the bladder. A nephrostomy tube is placed in the pelvis and a decapsulation is performed, with the object of decreasing intrarenal tension. Similar treatment of the opposite kidney may be necessary.

I had no fatal results, nor were there any deaths attributable to sulphonamide drugs in reports received from my colleagues.

Reports of Cases.

I should like now to outline briefly a few of my own cases and to quote case reports which have been handed on to me.

A male patient, aged seventy-six years, had been treated for *otitis media* with "M & B 693", nine grammes in twenty-eight hours. No instructions concerning fluid intake had been given, and practically no fluid had been taken. General abdominal tenderness developed, and he passed a few ounces of blood-stained urine in the next twenty-four hours. No urine was obtained on catheterization when he was admitted to hospital thirty-six hours later, that is, he had had about four days' anuria. Cystoscopy was performed under spinal anaesthesia. Innumerable crystals were found in the bladder and in the right ureteric orifice; the left appeared normal. A catheter was passed to the right kidney, and lavage with warm normal saline solution was carried out. It was impossible to engage the left ureteric orifice, owing to the intravesical projection of the large middle lobe of the prostate. After twelve hours, urine commenced to drain freely from the catheter, and overnight, in addition, copious urine was passed into the bed. He made an uninterrupted recovery.

A male patient, aged forty-seven years, had been treated for a septic hand—recurrence of old osteomyelitis—with sulphadiazine, twenty grammes in forty-eight hours. His fluid intake was low. Acute bilateral renal colic and vomiting and oliguria with blood-stained urine were present for the next forty-eight hours. For about twelve hours there was

a slight temporary response to the intravenous administration of normal saline solution with 5% dextrose. On his admission to hospital, the patient had been suffering from severe colic, vomiting and anuria for twenty-four hours. Immediate cystoscopy under spinal anaesthesia was performed. Innumerable crystals were found in the bladder and extruding from each ureteric orifice. Catheters were passed to each kidney with considerable difficulty, and the pelvis were washed out with sodium bicarbonate and normal saline solution. Immediately copious drainage occurred from the right kidney, but no drainage took place from the left. The intravenous administration of sodium sulphate solution was commenced, and after twelve hours urine was draining freely from both catheters. The patient made a complete recovery.

A female patient, aged seventy-three years, was treated for cellulitis of the foot with twenty grammes of sulphadiazine in four days. She then had pain in the right iliac fossa and vomiting. She was sent to hospital with the diagnosis of acute appendicitis. Two ounces of urine only were passed in the next forty-eight hours. On cystoscopy crystals were seen in the bladder and in the left ureteric orifice. The left ureter was easily catheterized; the catheter was obstructed in the intramural portion of the right ureter. The left catheter drained poorly, but four pints were passed *per urethram* in twenty-four hours. Complete recovery occurred.

A male patient, aged thirty-six years, was treated for tonsillitis with eighteen grammes of sulphathiazole in seventy-two hours. No alkali was given and fluids were not forced. He was given intravenously one litre of sodium sulphate solution. On the following day cystoscopy revealed ten ounces of urine in the bladder, with many crystals, and debris and crystals in each ureteric orifice. Both ureters were catheterized. The patient made a complete recovery.

A male patient, aged ten months, had been treated for pneumonia with an unknown amount of sulphanilamide. He had haematuria after two days and anuria on the following day. Vomiting occurred. Cystoscopy revealed crystals in the bladder, and crystals were obtained from each ureteric catheter. Each pelvis was washed out with sodium bicarbonate solution and sterile water. Fluids were given into the peritoneum and intravenously. The patient recovered.

A female patient, aged twenty-eight years, had received intermittent treatment for "pyelitis" for eight weeks with sulphadiazine and sulphathiazole. She was uraemic, and faint shadows were visible in both renal areas. Cystoscopy revealed crystals in the bladder and in both ureters. No urine drained from either catheter. Investigation revealed a congenitally hypoplastic kidney on the right side. An operation for left nephrostomy and nephrothotomy was performed. The patient recovered. She was instructed to return for right nephrectomy in six months, but did not do so. She reported to her local doctor in eight months, and was again given a sulphonamide. She was admitted to hospital with anuria, but the left nephrostomy opened spontaneously and she recovered.

A boy, aged five years, was treated for septic meningitis due to a penetrating wound of the eyeball with sulphapyridine, three grammes a day. He had haematuria after thirteen grammes had been given. Thirty-six hours later anuria supervened. Cystoscopy revealed crystals in the bladder. Both ureters were catheterized, and a large amount of urine was passed. Death occurred later from septic meningitis.

An elderly man had undergone suprapubic prostatectomy six months earlier. Two months after he left hospital epididymitis developed. Sulphathiazole was given (24 grammes in forty-eight hours). He suffered from violent bilateral renal colic and anuria. Cystoscopy revealed crystals in the bladder. It was impossible to catheterize the ureters, owing to technical difficulties. Sodium citrate solution was given intravenously without benefit. A pyelostomy was established on the right side, with the immediate secretion of large amounts of urine. The other kidney began secreting in a few days. The patient recovered.

A middle-aged woman had undergone left nephrectomy seven years previously for a calculus. A difficult operation was required for the removal of a residual cervix, and was followed immediately by anuria. Three days after the operation, cystoscopy revealed an impassable obstruction in the ureter, one inch from the bladder. A pyelostomy was established on the right side, and secretion began. Two days later sulphathiazole was given, fifteen grammes in two days. Anuria supervened. Blood was discharged from the pyelostomy tube, which was not blocked. The obstruction

was apparently tubular. Sodium citrate solution was given intravenously, with excellent effect, and complete recovery followed. The ureter regained patency later.

Comment.

A survey of these cases reveals examples of tubular, pelvic and ureteric obstruction. Relief of obstruction on one side was generally followed by secretory activity on the opposite side.

Conclusion.

In conclusion, if I may be permitted to point a moral, it would be to stress the mutual advantages of cooperation between members of a section and between sections. Whereas the comparative smallness of our community and of our clinics necessarily limits the amount of material available to one person, cooperation and clinical discussions considerably widen the field. We have in our hands one of the great advances of our age; but I would emphasize again the importance of continued watchfulness during the administration of the sulphonamides.

EXPERIENCES, DANGERS AND SEQUELÆ OF SULPHONAMIDE ADMINISTRATION IN CHILDHOOD.¹

By EDGAR H. M. STEPHEN,
Sydney.

THE experiences I am about to describe are collected from those of several members of the medical staff of the Royal Alexandra Hospital for Children, in addition to my own. I have spent time and effort in studying Wesley W. Spink's publication on "Sulphanilamide and Related Compounds in General Practice", in order to render this effort more complete. While duly conscious of the immense value of the sulphonamides in the treatment of many serious illnesses, I feel that they have been used far too extensively in the treatment of minor maladies and that this is not to the advantage of the patients. Complaints such as tonsillitis are readily amenable to treatment by other means, and an attack running a course not stifled by a sulphonamide builds up the resistance of the patient against early recurrences. A patient suffering from acute nephritis recently under my care had a history of several such recurrent attacks, apparently drastically curtailed, but with the unfortunate sequel of this serious illness. It may be that the courses of chemotherapy were too short to be completely effectual; but most of them cause a certain amount of inconvenience to the patient, and to my mind a degree of immunity obtained otherwise is often missed. A sharp rise of temperature at the onset of some mediocre attack does not justify an immediate resort to chemotherapy when there are insufficient grounds for the diagnosis of acute pneumonia. Once the course is begun it must be carried through for the usual period or the patient is rather the worse for its administration. The drugs have some toxic effects in certain cases, from which the patient has then to recover, and his state of ill health is thus prolonged unnecessarily.

At the risk of repeating what may be known to most, I shall give a *résumé* of Spink's admirable description of the mode of action of the sulphonamides. The primary action of the drug is bacteriostatic; that is, it brings about a diminution in the rate of growth of bacterial cells. Under some conditions the drugs may actually kill small numbers of microorganisms. In the human body the ultimate destruction of pathogens depends on two important factors, the bacteriostatic action of the drug and the defence mechanism of the host. The drug not only slows the rate of growth, but injures the cell, permitting the normal defence mechanism to destroy the microorganisms by such processes as phagocytosis and lysis. Because of variations in the efficiency of the normal defence mechanism, certain subjects require higher blood and tissue concentrations of

the drug than others. The sulphonamides do not interfere with the formation of antibodies, nor do they stimulate the production of immune substances. The use of sulphonamides does not contraindicate the use of specific antitoxins in diseases in which antitoxin is known to be of value.

Differences in solubility cause variation in absorption of the drugs. Absorption takes place in the upper part of the small intestine. Aqueous solutions, especially of sulphanilamide, are more rapidly absorbed than the drug in tablet form. A favourable feature is the facility with which the absorbed drugs are diffused to all tissues and body fluids.

Selection of Sulphonamide.

I find considerable variation in views on the selection of a sulphonamide. I associate success in treatment with the following preparations. In pneumococcal pneumonia the first choice is sulphapyridine, which I like to use in all severe cases; the second choice is sulphadiazine, when sulphapyridine is not tolerated, and for children aged two years and under. In *Bacillus coli communis* infections causing pyelitis or acute pyelonephritis sulphathiazole is the first preference and sulphanilamide the second. In infections with *Streptococcus hemolyticus* causing acute nephritis *et cetera* sulphanilamide is first and sulphathiazole is second. In staphylococcal infections sulphathiazole comes first and sulphadiazine second.

I remember with gratitude a child suffering from influenza meningitis, who responded rapidly to oral administration of sulphanilamide; but the treatment of the various types of meningitis I shall give on the lines followed in the public wards of the Royal Alexandra Hospital for Children by members of the honorary medical staff, who have had considerably more experience than I, with my limited number of patients in Wade House.

In meningococcal meningitis of average severity give sulphapyridine or sulphadiazine by mouth. The dosage is up to the full limit of the standard one grain per pound of body weight in the twenty-four hours, given in divided doses every four hours. The initial dose and second dose, on the day on which treatment is commenced, is double the quantity that is calculated to be given every four hours. If the patient cannot tolerate the drugs by mouth, a continuous intravenous drip administration of normal saline solution or glucose and saline solution is employed, and a solution of sulphapyridine is injected into the tubing at intervals of four hours. Usually improvement is manifest in forty-eight hours and the treatment can be continued by oral administration. This can be managed by using sulphadiazine in preference to the more nauseating sulphapyridine.

Meningococcal meningitis of the septicæmic type, in which the patient is gravely ill and purpuric patches are present, is treated with sulphapyridine and later with sulphadiazine, in conjunction with penicillin. A continuous intravenous drip administration of glucose and saline solution is instituted, and soluble sulphapyridine is injected into the tubing. After three days or so oral administration of sulphadiazine replaces the intravenous drip administration of sulphapyridine. Penicillin is given by the intramuscular and intrathecal routes. Intramuscular injections of 15,000 units are given every three hours until a total of 1,000,000 units is reached, when these injections are stopped. Coincidentally, 10,000 to 15,000 units are given intrathecally twice a day, and this dosage is continued for several days after cessation of intramuscular therapy. It has been proved of the utmost importance that the disease should be attacked in this "blitz" manner.

Pneumococcal meningitis is treated on exactly similar lines; but the prognosis is still an uncertain affair.

In influenza meningitis penicillin is of no avail. Treatment is again by the continuous intravenous drip administration of glucose-saline solution. Soluble sulphapyridine is injected into the tube every four hours for two or three days; later the treatment is carried on with sulphadiazine or sulphanilamide by mouth. *Haemophilus influenzae* type B specific antiserum (Commonwealth Serum Laboratories) is injected into the tubing. An initial dose of 90 to 120 cubic centimetres of the serum is given. The need for further serum therapy is determined by the clinical response, the

¹ Read at a meeting of the New South Wales Branch of the British Medical Association on April 26, 1945.

cell content, and the result attending cultivation from the cerebro-spinal fluid.

The report⁽¹⁾ furnished by the Children's Hospital, Melbourne, suggests that eight ounces of 5% glucose and saline solution be given at the rate of two ounces per hour; the serum is then added to the flask and administered in two hours. The flask is then refilled with more glucose and saline solution up to thirty ounces, and the subsequent rate of flow is decreased to one ounce per hour. As influenzal meningitis is characterized by a marked tendency to relapse, the administration of the sulphonamide selected has to be continued for up to twenty-eight days or six weeks. Blood examinations are necessary at frequent intervals, and blood transfusions are given as indicated.

Sulphaguanidine has had a successful career at the hospital in the treatment of colitis and infective diarrhoea. It is customary to administer a large dose as the initial one—two grammes for children under twelve months, and double that amount for children above that age. For subsequent doses one estimates the total quantity for the twenty-four hours at the rate of one grain per pound weight, giving the doses at intervals of four hours. Another method is to give 0.05 gramme per kilogram of body weight, *per diem*, starting the treatment with a single dose of 0.1 gramme per kilogram of body weight. I prefer the former method, as I find it a simple calculation. There is said to be some risk of liver damage if the drug is continued much over a fortnight. We have had no instance of this at the hospital.

Toxic Effects.

The most serious of the toxic effects is the occurrence of acute hæmolytic anemia. In the milder cases but one blood transfusion may be required for recovery to be achieved, but in more severe cases transfusion may need repetition. The intravenous administration of glucose with insulin has also proved of great value. Apparently certain subjects are hypersensitive to sulphonamides. Dr. P. L. Hipsley reported in THE MEDICAL JOURNAL OF AUSTRALIA of May 9, 1942, the history of such a patient, who had been given sulphapyridine.

The child was aged three years, and was suffering from tonsillitis. She was given a dose of approximately two grains, which was repeated in six hours. A third dose, six hours later, was vomited. Soon after this, she became intensely anæmic and jaundiced, and had pronounced hæmaturia. Her blood picture was reported by Dr. Eva Shipton to be that of an acute hæmolytic anemia. The count was repeated several times. She was given four transfusions of ten ounces of citrated blood by the drip method and made a good recovery. The urine contained a few red cells only and some epithelial cells. Numerous short, cylindrical bodies, somewhat resembling casts, were also present; they were probably composed of acid hæmatin.

Occasionally the administration of sulphanilamide has been reported as being followed by agranulocytosis, hæmolytic anemia and acute necrosis of the liver, with a fatal termination. The only toxic effect noted at the hospital was cyanosis, which was more readily excited by sulphanilamide than by other sulphonamides.

Drug fever occurs from time to time, usually after the drug has been administered for about five days. Sulphathiazole is credited with a special tendency to this effect and also to the occurrence of a rash like *erythema nodosum*.

Serious nausea and vomiting have occurred, most frequently in patients taking sulphapyridine. By young children the drugs powdered, mixed with a pinch of bicarbonate of soda and given with lemon syrup, are tolerated well. Loss of appetite and occasionally diarrhoea, headache, dizziness, tinnitus and mental depression have at times been noted.

Hæmaturia, sometimes macroscopic in degree, has been encountered a number of times. Hæmoglobinuria occurred in one case in which sulphathiazole was being taken.

Skin eruptions of various types may occur after five to seven days of administration of the drug. As in some instances the areas affected are those exposed to sunlight, the patients are not nursed out of doors. Anæmia during sulphonamide therapy is seen more frequently in children than in adults. It is due to increased destruction of red cells and to a disturbance in the formation of hæmoglobin.

Sulphanilamide and sulphapyridine are more prone to cause this effect than are the other sulphonamides.

Depression of the level of white blood cells is less frequent. The number of neutrophile cells is most commonly reduced. Spink advises the use of 40 cubic centimetres of "Pentnucleotide" by intramuscular injection should agranulocytosis develop, and discontinuance of treatment with the drug if the level falls below 3,500 to 4,000 cells per cubic centimetre.

Conjunctivitis and scleritis are seen occasionally, especially when sulphathiazole is being used.

Another toxic manifestation is pronounced leucocytosis.

While under treatment with sulphonamides, children in the hospital have shown the following symptoms: (i) anorexia; this has been a common occurrence, and is especially pronounced among the very young who have been receiving sulphapyridine; sometimes vomiting also occurs; sulphanilamide has proved next in toxicity; (ii) cyanosis, mostly with the same two drugs; (iii) rashes, morbilliform and otherwise; (iv) macroscopic hæmaturia; (v) anuria, recorded once; (vi) acute hæmolytic anemia, which has occurred less than once in a year; but one child receiving sulphapyridine did not survive. It is considered that increased experience in the use of these drugs and careful watching for the known signs of toxicity have been successful in preventing such occurrences.

It is worth while recording a striking cure that followed the accidental administration of an excessive dose in a limited period of time.

The child was gravely ill with meningococcal septicæmia, with hæmorrhagic spots. Intravenous drip therapy was instituted. Inadvertently seven grammes (14 tablets) of sulphapyridine in solution were instilled into the patient in two hours. The child became blue and was almost uncontrollable. Twenty-five hours afterwards, the concentration of the drug in the blood was 21 milligrammes per 100 cubic centimetres. By way of treatment the child was given a solution of glucose intravenously. A rapid recovery was the final result.

In two or three other patients uncontrollable restlessness has developed while soluble sulphapyridine was being administered intravenously, and the infusion had to be discontinued.

Summary.

One may summarize the position as follows:

1. Sulphadiazine, with its low toxicity, is the most popular of all the sulphonamides, and in the opinion of most is as efficacious as any of them.
2. When it is desired to use intravenous therapy sulphapyridine must be used, as it is the only member of the group available to us in a soluble form up to the present time.
3. In the case of certain seriously ill patients, especially while receiving intravenous therapy, the concentration of the drug in the blood or cerebro-spinal fluid should be estimated. Up to 10 milligrammes per 100 cubic centimetres is the optimum figure, except in the case of sulphadiazine, of which 10 to 15 milligrammes per 100 cubic centimetres are desirable. These figures are only a standard for guidance, as in certain instances favourable results are achieved at a lower standard, and on the other hand success may not follow the maintenance of the standard or even a higher concentration.
4. It is permissible to change from one preparation to another.
5. Whenever possible, administer the sulphonamide by mouth.
6. The major excretory channel is the kidneys. Caution must be exercised in prescribing sulphonamides for patients whose renal function is impaired.
7. When toxic symptoms arise, elimination of the drugs is aided by the administration of liberal amounts of fluids.
8. Seriously ill patients require large initial doses.

Conclusion.

In the early days of sulphonamide therapy one was warned not to use onions, egg yolk, aspirin or salicylates. Now apparently one is at liberty to use any of these; but sulphates such as those of sodium and magnesium are to

be avoided. Sulphonamides have not proved of value in diphtheria, in the common cold, in influenza, in tuberculosis, in acute rheumatism or in poliomyelitis, unless some intercurrent infection has intervened.

Acknowledgements.

I have to thank Dr. Gertrude Geikle and two or three of my friends amongst the physicians for most useful contributions from their experiences.

Reference.

⁽¹⁾ E. K. Turner: "A Further Report on the Treatment at the Children's Hospital, Melbourne, of Influenzal Meningitis with Sulphonamides and Type-Specific Serum", *THE MEDICAL JOURNAL OF AUSTRALIA*, March 3, 1945, page 219.

ELECTRICAL ANÆSTHESIA.

By S. ROSE and D. RABINOV,

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If the cerebral cortex of an animal is stimulated repeatedly by an electric current, the excitation spreads (by facilitation) to the whole cortex. This spread of excitation is followed by inhibition. If this inhibition could be maintained then sleep might be produced; according to Pavlov⁽¹⁾ sleep is a spread of inhibition in the cortex. The purpose of our experiments was to determine the possibility of producing anaesthesia by the passage of electric currents through the central nervous system, and also to find the nature of the current which produced the best results. The first indication that electrical anaesthesia could be produced was suggested by Leduc in 1906,⁽²⁾ and while our experiments were being completed an article on similar work was published.⁽³⁾

METHOD.

Various electrical devices in the nature of oscillators and peak formers⁴ were used to produce an intermittent direct current (Figure 1). Variation could be produced in (i) the frequency of stimulation, (ii) the time duration of each stimulation, (iii) the shape of the curve, the current growth usually being logarithmic, and (iv) voltage, from 0 to 240 volts.

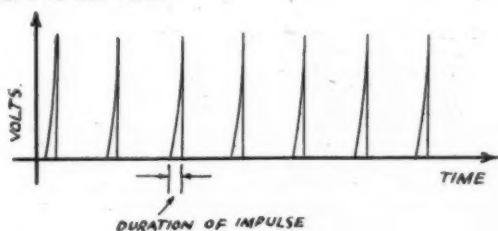


FIGURE 1.
Wave form of stimulator.

Experiments were carried out on rats, rabbits, cats and monkeys. Plate electrodes of one square inch with saline solution were applied to shaven head and tail.

RESULTS.

General Effects on Animal.

As the voltage was increased tetanus was produced and the animal fell on its side. During this stage both fore and hind limbs were extended, the latter the more strongly. The respiratory muscles were also in a state of tetanus and the breathing was forced and accompanied by irregular choking sounds. The eyes were glassy in appearance and turned upwards and inwards. The animal showed no painful reactions. After twenty to thirty seconds of tetanus the animal passed into a relaxation stage in which the muscles became relatively flaccid—the hind limbs were still in a state of slight tonic extension. The corneal and pupillary reflexes were absent and there was no reaction to what would normally be a painful stimulus. The breathing became quieter and more regular. When the

voltage was reduced to zero the animal shook its head, straightened its body and attempted to move away in a normal fashion. The hind limbs were much weaker than usual and unable to support the body weight, so that the animal dragged on its hind legs. The limbs recovered within fifteen minutes. The animal after this electrical treatment was much quieter than previously.

Results of Different Methods of Increasing Voltage.

(a) The voltage was slowly increased until tetanus was first produced. The voltage remaining constant, the animal recovered (being relaxed and awake) within two minutes. The voltage was again increased until tetanus followed by recovery was elicited. The above sequence with successive increases in voltage was repeated. When 70 volts were reached, the animal relaxed from its tetanus but remained anaesthetized.

(b) The voltage required for anaesthesia of a particular cat having been determined by the above method, the voltage was increased in thirty seconds to a value of 25 volts higher than that required for anaesthesia. Severe tetanus was produced, which after another twenty to forty seconds had almost disappeared. The voltage was slowly decreased until the animal first gave an indication of consciousness by blinking its eyelids. It required only a five-volt increase again to produce anaesthesia. This is the threshold anaesthetic value and any decrease in voltage below this will enable the animal to awaken.

Effect of Frequency.

Four cats were anaesthetized under the conditions of 60 volts, 100 cycles per second. The frequency was then gradually increased. At 120 cycles per second the animals awoke and either a reduction in frequency or an increase in voltage was required to anaesthetize them. It seems that the higher the frequency above 100, the greater is the requisite voltage. This may be due to the fact that facilitation of neurones in the cortex occurs best at such a frequency or perhaps lower. Unfortunately lower frequencies could not be obtained with the oscillator employed. There seems to be a negligible effect on the anaesthesia produced when the closure times for each stimulation were varied from 1/750 second to 1/1250 second. It appeared that a slightly lower voltage was required when the closure time was about 1/950 second.

Effect on Respiration.

A rubber bag in which the pressure could be varied was wrapped around the thoracic region of a cat. The bag was connected to a tambour and respiratory recordings were

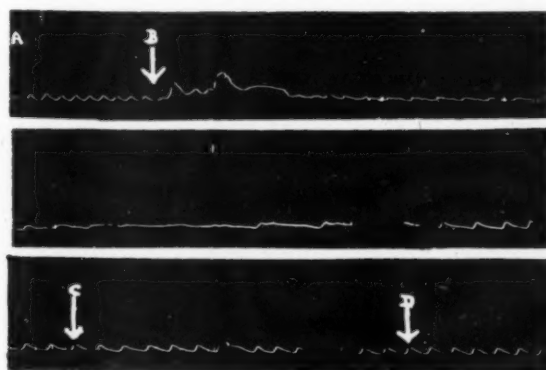


FIGURE 2.

The effect on respiration of a kitten during the various stages of anaesthesia. A-B, normal respirations; B-C, current on, animal in tetanus; C-D, current on, animal now relaxed. At D the current was turned off, and it will be seen that there is very little alteration in the respiratory movements.

made by a kymograph. During the initial period of tetanus the breathing was forced and irregular. When the animal relaxed, however, the breathing returned to normal, except that the respirations were slightly slower (Figure 2).

¹ By courtesy of the Council for Scientific and Industrial Research, Melbourne.

To aid in these respirations the animal attempted to use to a great extent the abdominal and forelimb musculature. Fluctuating variations of voltage produced temporary disturbance of respiration. This occurred during the period of the change and for a short while after.

Effect on Blood Pressure and the Heart.

The blood pressure was recorded from a cannula in the carotid artery. Because no suitable method could be found of recording the blood pressure of an animal such as a cat not anesthetized, the experiments were of two types.

1. A cat was anesthetized with 50 volts, 100 cycles per second. The carotid artery was then dissected and a cannula inserted. The voltage was increased and this caused a rise in blood pressure, while a decrease in the voltage caused a lowering of the blood pressure. These results are shown in Figure III. Note that in this experiment the immediate effect on the blood pressure is not shown, because the animal was already anesthetized by the electric current.

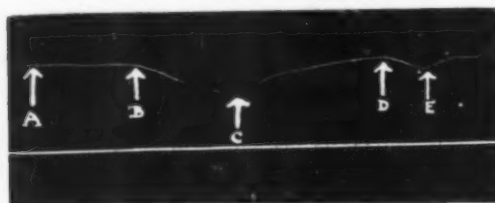


FIGURE III.

The effect on blood pressure of an anesthetized kitten (50 volts, 100 cycles per second) when the voltage is varied. A-B, blood pressure while the animal is anesthetized under the above conditions; at B the voltage was reduced to one-half; at C it was increased to its original amount; at D it was reduced by 12 volts.

2. A cat was given 200 milligrammes of "Nembutal", and when it was anesthetized a cannula was inserted into the carotid artery, electrodes were applied and the current was passed; a rise and a fall in blood pressure were obtained by increase and decrease in the voltage respectively (Figure IV).

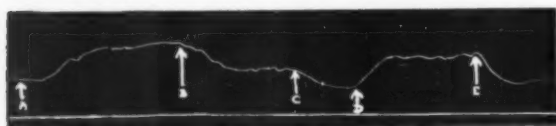


FIGURE IV.

The effect on blood pressure of an anesthetized rabbit (200 milligrammes of "Nembutal") with variation in voltage. A, blood pressure of animal asleep after "Nembutal"; at A, 90 volts were applied; at B, voltage decreased to 45; at C, decreased to 0; at D, increased to 90; at E, decreased to 0.

Experiments to Determine the Factors Causing the Rise in Blood Pressure.

The splanchnic nerves (of both sides) in an anesthetized cat were cut and the effects on the blood pressure when the current was applied were again recorded. A rise in blood pressure slightly smaller than in the previous experiment was again obtained. This rise in pressure could not be due to the splanchnic stimulation.

The splanchnics and vagi (of both sides) in an anesthetized cat were cut. The rise in blood pressure was again obtained on passing the current, but the rise was not so great as in the first experiment.

The splanchnics, vagi and stellate ganglia (of both sides) were cut. The blood pressure was raised insignificantly when the voltage was increased.

A rabbit was anesthetized with "Nembutal" and artificially respired by insufflation through a tracheal cannula. The thorax was opened and the heart was exposed. As the current was turned on and the voltage was increased, the heart appeared to beat more forcibly and a few extrasystoles occurred, but there appeared to be no increase in the heart rate. After the current had been passed for a short period the heart's movements returned to normal. A hook was then passed through the ventricular musculature at the apex of the heart and connected to a lever which

recorded the heart's movements. Very little alteration in the heart's movements was observed when the voltage was increased and decreased, and the tracings merely showed a slight transient fluctuation (Figure V).

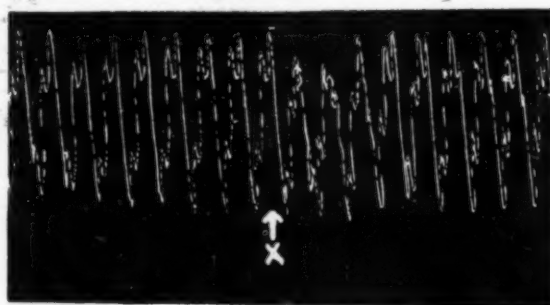


FIGURE V.

The effect of the current on heart movements of an anesthetized rabbit. At X the current was applied, and only a slight transient fluctuation was observed.

Phenomena of Adaptation.

Two animals were kept unconscious for about twenty minutes and recovered (being relaxed and awake) when the current was cut off. The current was then again increased, and the preanesthetic tetanus produced in this case was much less than on the original occasion.

Two rats were rendered unconscious by an electric current at 60 volts. After half an hour of anesthesia the animal began to awaken and it was necessary to increase the voltage to maintain sleep. At the end of three hours, by gradual increases in voltage strength, the animal required 120 to 140 volts for anesthesia.

Two rats were anesthetized for ten minutes each day over a period of five days. At the end of this time a 20 volt rise over the original voltage was required to produce sleep.

Individual and Species Variation.

There is a considerable difference in the effect produced on animals of different species. (a) The rat develops a greater tension in its muscles and in general the tetanus is not lost during any stage of the anesthesia. (b) The rabbit relaxes its forelimbs and quite often its hind limbs, but is more likely to be killed during anesthesia than other animals. (c) The cat relaxes completely and usually shows no after-effects.

It will be noticed that as the animals used were higher in the phylogenetic scale, so were the results more satisfactory, in that less tetanus and more complete anesthesia were obtained. In the monkeys there was very little preliminary tetanus. By means of a special amplification system it was shown that little change in the heart rate occurred. During the induction period—that is, when the current is being turned on—the heart rate may quicken and the beat become more feeble, but the condition soon returns to normal when the voltage is changed to the optimum value, which is 75 volts.

Individual variations were also noticed. Six rats were anesthetized; the voltage required did not depend on the weight of the animal; whereas five of the six rats required a voltage ranging from 50 to 90, the smallest of the group required over 140 volts. A few of the rabbits, having been anesthetized for about thirty minutes, went into convulsions, which were more readily elicited if the frequency or voltage was varied, or if an attempt was made to flex passively the extended hind limbs of the animal.

The Effect on General Behaviour and Conditioned Reflexes.

Electrical currents were applied for ten minutes on five consecutive days to rats which had previously been trained to swim up a darkened but not up a lighted pathway when placed in a tub of water.¹ Immediately after the last treatment they were retested for this behaviour. Only one

¹ Kindly supplied by Professor Agar, Department of Zoology, University of Melbourne.

failed to remember that it should go up the darkened gangway, the others being completely normal in this respect. The rats were retested on the following day and all were successful—even the rat which on the previous day had entered the wrong gangway.

DISCUSSION.

In this paper we have recorded the effects of an intermittent current (100 cycles per second) on various animals, electrodes being applied to the frontal and sacral regions. It has been found that a condition closely resembling anaesthesia is readily produced. The optimum voltage was 70 for most species, and it was found necessary to raise the voltage fairly rapidly from 0 to 90 within one minute and then to reduce the voltage to the optimum for anaesthesia. The frequency most effective was 100 cycles per second.

There was some species variation, in that muscular relaxation was most evident in the monkey, while in the rat the muscles remained in a state of powerful tetanus. This technique may be applicable as a means of anaesthetizing humans, but this use has not yet been developed. However, it appears probable that satisfactory results would be obtained, for it is noticed that the higher the animal is on the phylogenetic scale, the better is the anaesthesia produced.

During the induction stage rigidity develops, affecting all limbs. Laryngeal effects are evidently produced, since a crowing sound is heard. The pulse rate is little affected, occasional slowing being observed.

There appeared to be no untoward effects, since the breathing and heart rate of the animals after treatment were normal and the animals looked quite well. Slight paralysis of the hind limbs lasting a quarter of an hour was noted. No inhibitory effects were observed on conditioned reflexes.

SUMMARY.

1. It is possible to anaesthetize animals without apparent pain by suitable intensity and frequency of an electrical current applied to the nervous system.
2. No permanent damage was produced, either mental or physical, and there was an almost immediate recovery on the withdrawal of the electric current.
3. There is considerable individual and species variation in the effects produced.
4. Provided the current is controlled and careful observations are made on the animal, it is possible to produce anaesthesia with some degree of safety. The dose required for anaesthesia is much below the lethal dose and has the great advantage that it can be readily varied.

ACKNOWLEDGEMENT.

We wish to thank Professor E. R. Trethowie for his encouragement and advice during the course of these experiments.

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Reports of Cases.

RECURRENT APPENDICEAL ABSCESS.

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THE cause of an appendiceal abscess is perforation of an acutely inflamed appendix obstructed usually by a fecolith. When rupture occurs, the purulent contents, which may include fecoliths, escape into the appendiceal bed. These abscesses are usually retrocaecal or pelvic, because the diagnosis of appendicitis in these regions is often delayed.

It is now recognized that the correct and ideal treatment of appendiceal abscess is incision and exploration, together with removal of the offending appendix and any escaped fecoliths.⁽¹⁾ Technical difficulties or poor general condition of the patient may allow only drainage of the abscess, and in such cases the appendix is removed later after a somewhat arbitrary period of three months.

Should treatment fall short of the ideal, so that the abscess has only been drained without removal of the cause, or no operation has been performed at all, then the patient runs the risk of further abscess formation with its attendant dangers and morbidity, as well as economic loss due to further and prolonged stay in hospital.

A discussion of thirteen cases of recurrent appendiceal abscess is presented. Ten of the patients were male and three were female. The average age was thirty years, the youngest patient being aged seven years and the eldest sixty years. In each instance this was the first recurrence, and the time interval between abscesses averaged one hundred weeks, the shortest period being four weeks and the longest ten years.

At the original illness, four patients underwent drainage of the abscess with complete (Cases I and II) or incomplete (Cases III and IV) removal of the appendix, six (Cases V to X) underwent drainage of the abscess only, and three (Cases XI to XIII) had undergone no operation. In each instance it was evident from the history and later findings that the cause of the original abscess was rupture of an appendix, the seat of acute obstructive appendicitis. Obstruction was caused in nine instances by impacted fecoliths, in one by a carcinoid tumour (Case IX) and in one by a fish bone (Case X). The cause of the obstruction was not apparent in Cases III and IV.

The commonest cause of recurrent abscess was further inflammation in a still obstructed, perforated appendix; this occurred in nine cases (Cases V to XIII). Free-lying fecoliths were the cause in two cases (Cases I and II), though the appendix had been previously completely removed. Incomplete removal of the appendix was the cause in two cases (Cases III and IV).

In every case the abscess recurred in its original position, being retrocaecal in eleven cases and pelvic in two (Cases VII and XI).

There was a history of previous appendiceal abscess in every case. In three cases only (Cases VI, X and XIII) had any symptoms occurred in the intervening period. These consisted of vague aches and sharp pains recurring at irregular intervals.

Pain, varying from a mild ache to a severe sharp pain, appeared in the right iliac fossa when retrocaecal abscesses recurred. The pain was generalized (Case XI) or situated in the lower part of the abdomen (Case VII) when a pelvic abscess recurred. The length of time between the onset of pain and the clinical evidence that the abscess was present was uncertain, as in all cases the abscess was palpable on the patient's admission to hospital. The period appeared to vary from six to twenty-four hours or more.

A more or less tender mass was palpable in each patient, in the right iliac fossa in eleven and in the pelvis in two. In those who had been previously operated upon, the main site of tenderness was round the incision.

There were no constitutional disturbances in three cases (Cases II, VI and IX), but in the others the temperature on the initial examination varied from 99° to 103° F.

Bowel symptoms were absent, except in Case VII; this patient suffered from diarrhoea and rectal tenesmus due to the pelvic position of the abscess.

Leucocyte counts were not found necessary, as the diagnosis was obvious in each case.

Facilities for radiography were not available in every case. Plain radiograms of the abdomen in Cases II, VI, VII and X revealed a calcified fecolith in Case II and a fish bone in the right iliac fossa in Case X. In the other cases radiographs revealed no abnormality, except the soft tissue shadow of the abscess in Case VII.

The diagnosis was based on the previous history and on the finding of a tender mass. There is only one common condition that may mimic a recurrent appendiceal abscess, and that is an incarcerated omentocoele in the original incision, especially when drainage of the abscess has been performed through the wound. This is characterized by a painful, tender swelling, which may be accompanied by a rise in temperature and even by neutrophilia. Usually the only means of differentiation is by operation.

Operation was performed in all cases as soon as the diagnosis was made, except in Cases XII and XIII; these patients were almost moribund on their admission to hospital.

The abscess was approached by the most direct route, and in those cases in which a previous operation had been performed, this was through the original incision. In each instance, the abscess cavity was able to be opened without the peritoneal cavity's being traversed. In the cases of retrocaecal abscess, the route went below and lateral to the caecum. The abscess cavity was opened by careful finger dissection and the faecal smelling pus was sucked out. The cavity was then explored by the finger and by vision with careful retraction.

In Cases I and II faecoliths lying free in the abscess cavity were picked out, and in Cases III and IV inflamed appendiceal remnants were removed.

In Cases V, VI, VIII, IX and X the appendix was found to be perforated beyond an obstruction, which was a faecolith in Cases V, VI and VIII, a carcinoid tumour in Case IX and a fish bone in Case X. The appendix was able to be removed with ease in these five cases, the finger carefully separating it from the posterior wall of the caecum and the posterior abdominal wall. During this removal, the general abdominal cavity was opened in two cases (Cases VIII and IX), as the base of the appendix was not involved in the inflammatory process. The peritoneum was sutured as soon as the appendicectomy had been performed. The appendix was removed by ligating the mesoappendix with multiple ligatures, and by ligating the base after crushing it. Chemicals were not applied to the stump, nor was it invaginated, as in any case the caecal wall was too thick and hemorrhagic. In Case VI the appendix had to be removed in the retrograde manner. Sulphonamide powder was not insufflated, but sulphonamide was given orally in the early post-operative period, sulphamerazine now being the drug of choice.

Drainage of the abscess cavity was performed through a stab-wound in all the foregoing cases, its position depending on the position of the abscess. The main wound was then sutured in layers by interrupted catgut sutures, the superficial fascia being drained by rubber glove drain.

In two cases drainage of the abscess only was able to be employed. In Case VII the pelvic abscess was too large and the wall so thick and irregular that the appendix could not be identified. Three months later, appendicectomy was performed through a separate paramedian incision. In Case XI the patient was too ill to allow more than the making of a small suprapubic incision to release the pus. Appendicectomy was performed four months later through a McBurney incision.

The two patients (Cases XII and XIII) who were moribund on their admission to hospital, and so were not operated upon, died of suppurative portal pylephlebitis, confirmed at autopsy.

The nine patients who had the cause of the abscess removed at the time of drainage has an uneventful convalescence, save in four cases (III, VI, VIII and X), in which a mild wound infection supervened. In Case III *Bacillus coli* and *Bacillus proteus* were isolated from the wound, but facilities for pathological investigation were unavailable in the others. The main wound usually healed in about fourteen days and the stab-wound in about three weeks. When infection supervened, healing was delayed for a further week. It was noticed that in the two cases in which the abdominal cavity was opened there was no evidence of spread of infection.

In Cases VII and XI, in which drainage of the abscess only was performed, a purulent discharge persisted for as long as three months. Appendicectomy was then performed through a different incision. In Case VII the wound became mildly infected with *Bacillus coli communis* and *Bacillus proteus*. Otherwise convalescence was uneventful.

Follow-up investigations varying from three weeks to two years showed that all patients were free of any further trouble from this cause.

Case I.

A girl, aged fourteen years, had an appendiceal abscess drained with removal of a ruptured appendix. No note was made as to the presence or absence of faecoliths. The wounds healed; but four weeks later she began to suffer from severe pain in the right iliac fossa, her temperature rising to 100° F. Twenty-four hours later a tender mass was palpable there. Operation was then performed through the original McBurney incision, and a retrocaecal abscess, containing much faecal-smelling pus, was opened lateral to the caecum. Two large soft faecoliths were found in the abscess cavity. They were removed and the cavity was drained. Convalescence was uneventful, and follow-up inquiry two years later showed that she had had no further trouble.

Case II.

A woman, aged twenty-two years, had a retrocaecal abscess drained, with removal of a gangrenous appendix which had ruptured distal to an impacted faecolith. Two years later, she had a slight pain in the right iliac fossa, and a large mass was found there forty-eight hours later. She was apyrexial throughout her illness. A plain X-ray film of the abdomen revealed a small calcified mass in the right iliac fossa. The abscess was opened through the original McBurney incision, and a large, hard, calcified faecolith was removed. The abscess was drained in the usual manner. Convalescence was uneventful, and when examined twelve months later the patient was well.

Comment.

Even though the ruptured appendix contains a faecolith, search of the abscess cavity must be made for any others that may have escaped. This must be done especially when a ruptured appendix is found which has no apparent obstruction.

Case III.

A male patient, aged forty years, had an appendiceal abscess drained through the right iliac fossa; he said that his appendix was removed at the same time. Two years later he suffered from acute pain in the right iliac fossa, with a temperature of 99° F.; a large, tender swelling was found there twelve hours later. This was opened through the original McBurney incision, and much faecal-smelling pus was evacuated from behind the caecum. Two inches of acutely inflamed terminal appendix were found to have been left, *in situ* attached to the posterior wall of the caecum by its mesoappendix. This was ligated and the appendiceal remnants were removed. No faecoliths were present. The abscess cavity was drained in the usual manner.

Convalescence was complicated by a mild wound infection due to *Bacillus proteus* and *Bacillus coli communis*, but the wounds were completely healed in three weeks. Further follow-up investigation was not possible.

Case IV.

A male patient, aged twenty-three years, had an appendiceal abscess drained with removal of the appendix. Twelve months later he suffered from severe pain in the right iliac fossa, and his temperature rose to 100° F. A large mass was discovered there twenty-four hours later. A plain X-ray film of the abdomen revealed no abnormality. The abscess was opened through the original McBurney incision, and much foul pus was evacuated. About two inches of the base of the appendix had been left behind at the previous operation. It was acutely inflamed, though no obstructive cause was found. It was removed and the abscess was drained. Convalescence was uneventful, and six months later the patient was well.

Comment.

When removing a friable appendix, care must be taken that no remnants are left behind.

Case V.

A boy, aged fifteen years, had a retrocaecal appendiceal abscess drained through a stab-wound below a McBurney exploratory incision. Convalescence was uneventful, and he was instructed to report three months later for removal of his appendix. However, six weeks after operation he suffered from severe pain in the right iliac fossa. His temperature rose to 101° F., and a large mass developed twenty hours later. This was opened through the previous incision, and a large, foul-smelling, appendiceal abscess was evacuated. It was due to an acutely inflamed appendix which had ruptured distal to an impacted faecolith. This perforation was surrounded by much exuberant granulation tissue, showing that this was the cause of the first abscess. The appendix was easily removed and the abscess cavity was drained. Convalescence was uneventful, the wounds healing in three weeks. When examined twelve months later the patient was well.

Case VI.

A male patient, aged thirty-five years, had an attack of "appendicitis" lasting for three days. He was operated on through a McBurney incision, through which the abdomen was drained. Pus drained away for two weeks, and the wound then gradually healed. Although he admitted that he was told that his appendix had not been removed, he assumed "that it had drained out through the wound".

During the next few years he had some mild aching and pain in the right iliac fossa, which were said to be caused by adhesions. Ten years after his original operation he had a severe attack of pain in the right iliac fossa lasting for two days. No rise in temperature occurred. Examination revealed a tender mass deep to the scar of a long-angled incision through which tube drainage had obviously been employed. A plain radiograph of the abdomen revealed no abnormality.

Operation through the wound disclosed a large retrocaecal abscess, with a ruptured gangrenous appendix containing a faecolith. It was retrocaecal and retroperitoneal, so that the abdominal cavity was not opened. Appendicectomy was a little difficult and was performed in the retrograde manner, the abscess cavity then being drained. Convalescence was normal save for a mild wound infection. When examined three months later the patient was well.

Case VII.

A male patient, aged thirty-five years, had had a pelvic abscess caused by acute suppurative appendicitis. This was drained suprapubically, the appendix being left *in situ*. Drainage persisted for six weeks. He was then told to report back in three months, but said later that he had not been told the reason. He did not do so, as he felt well, and he was under the impression that his appendix had been removed.

Twelve months later he again suffered from severe lower abdominal pain and diarrhoea with rectal tenesmus. His temperature rose to 102° F., and four days later he was found to have an enormous pelvic abscess which felt like a full bladder on abdominal palpation. Rectal examination showed that it had displaced his rectum to the left. A plain X-ray film of the abdomen revealed only the soft tissue of the abscess.

The abscess was opened through the previous suprapubic incision and an enormous amount of foul pus gushed forth. The abscess cavity was palpated by the finger, but it was so large and the walls were so thick and irregular that no appendix could be felt. A drain was placed in position, and it was three months before drainage from the cavity ceased. The appendix was then removed with some difficulty through a paramedian incision. It was found that the abscess was due to a perforation in the distal half of a pelvic appendix obstructed by an impacted faecolith. The peritoneal cavity was of necessity opened in this operation, as the proximal half of the appendix was not involved in the inflammatory process. Numerous adhesions were found in the pelvis where the abscess had been, and there was some difficulty in mobilizing the distal half of the appendix. The abdomen was not drained, but superficial glove drainage of the wound was instituted. Convalescence was uneventful save for a mild wound infection due to *Bacillus coli communis* and *Bacillus proteus*. When examined six months later the patient was well.

Comment.

If the appendix is not removed at the first operation, it must be firmly impressed on the patient that he still has it, and that it is likely to cause dangerous complications unless it is removed. To many patients, an appendiceal scar is synonymous with a lost appendix.

Case VIII.

A male patient, aged forty years, developed a quiet retrocaecal abscess from a ruptured appendix. On the eighth day of his illness his temperature rose to 100° F., and he commenced to suffer from severe pain in the right iliac fossa with vomiting, so that operation was decided upon.

The abdominal cavity was entered through a McBurney incision and a mass was located behind the caecum. From the operation notes, it was learned that no attempt had been made to drain the abscess, but a tube was merely placed down to the region of the caecum and brought out through the parietal wound. He was very ill for the next three days, with a temperature of 103° F., continuous vomiting and severe pain in the right iliac fossa. Penicillin was administered intramuscularly and sulphathiazole by mouth. The intestine was drained by a Miller-Abbott tube and he received fluids intravenously. On the third day he felt something "burst" in the abdomen, and pus gushed out of the tube, causing rapid relief of his symptoms.

When he was examined one month later, his wound was almost healed. However, he again suffered from severe pain in the right iliac fossa, which was tender and rigid. Operation was performed through the original wound, a large abscess being opened. In it was an acutely inflamed appendix, perforated at its tip and containing an impacted faecolith in its mid-length. The appendix was removed, the

abdominal cavity being opened, as the base of the appendix was not involved in the inflammatory process. The abscess cavity was drained in the usual manner. Convalescence was uneventful, and the wounds had healed in three weeks after a mild superficial inflammation. Further progress could not be ascertained.

Comment.

It is most dangerous to open an abdomen and merely place a tube down to and not into an abscess. The abscess does not always burst into the tube. It is better to perform no operation at all.

Case IX.

A male patient, aged twenty-five years, had an appendiceal abscess drained. Drainage persisted for four weeks, and he was then well for twelve months. He then again suffered severe pain in his right iliac fossa. His temperature did not rise, but he vomited. When he was examined six hours later, a small mass was palpable in the right iliac fossa. A plain radiograph of the abdomen revealed no abnormality.

Operation through the original McBurney incision disclosed a small retrocaecal abscess surrounding an appendix which was acutely inflamed and perforated at its tip. The appendix was removed, the abdominal cavity being opened when its base was approached. It was then seen that the base of the appendix adjacent to the caecum was the seat of a large, yellowish tumour, which had completely obstructed the appendiceal lumen. The abscess cavity was drained in the usual manner. Convalescence was uneventful, and the patient was well when examined three months later.

Pathological examination disclosed that the tumour was a carcinoid tumour. There was no evidence of caecal or meso-appendiceal involvement, and it was well encapsulated.

Comment.

Fortunately these tumours are not malignant, else the twelve months' delay might have been fatal. Exploration of the abscess in the first instance would have disclosed the tumour.

Case X.

A male patient, aged fifty years, had an appendiceal abscess drained through a McBurney incision. The wound drained for six weeks before it healed. He then noticed at irregular intervals attacks of sharp pain in the right iliac fossa. Eight months after operation these became accentuated, and a large mass appeared in the right iliac fossa. His temperature rose to 103° F. and he felt very ill. A plain X-ray film of the abdomen disclosed a small, curved, calcified body in the right iliac fossa.

Operation through the original wound revealed a large retrocaecal abscess full of foul pus. The appendix was found to be gangrenous, with a perforation at its tip. It was completely obstructed in its mid-length by a large fish bone, the sharp end of which had also perforated its coats. The appendix with its contained fish bone was removed and the abdominal cavity was not opened. Drainage was instituted in the usual manner.

Convalescence was complicated by a mild wound infection, but the wounds had both healed after three weeks. Six months later the patient said that he had no further symptoms.

Comment.

Exploration of the abscess at the first operation would have disclosed the fish bone.

Case XI.

A boy, aged seven years, lived in an isolated district. He suffered from what was obviously an attack of acute appendicitis, which was treated as a "stomach ache" by his parents with castor oil and hot fomentations. He was first examined by a doctor on the seventh day of his illness, and a large, tender mass was found low in the right iliac fossa. This was allowed to subside and was said to be absent two weeks later. Two weeks later still, he suffered from severe generalized abdominal pain, his temperature rose to 102° F., and a large pelvic abscess was found. This appeared to track up towards the right iliac fossa. He was admitted to hospital, and was found to be so ill that the only operation that could be performed was to incise the abscess suprapubically under local anaesthesia. Much foul pus gushed forth. His condition improved for a week, and then another locus of the abscess was found pointing into the rectum, through which it was opened.

His condition then improved, and four months later his appendix was removed, a McBurney incision being used. It was a long pelvic appendix containing a faecolith in its distal third, which was surrounded by adhesions which had

sealed off a large perforation at the tip. Appendicectomy was performed and the abdomen was closed without drainage. The superficial layers of the parietal wound were drained by a glove drain.

Convalescence was uneventful, and he was well when examined three months later.

Comment.

This case discloses the admitted dangers of conservative treatment of appendicitis in children, especially when aided by castor oil.

Case XII.

A male patient, aged forty years, had a history of having had an appendiceal abscess treated by conservative measures. He said that he had been ill for one month, and was then discharged from hospital. He did not return for operation as instructed, as he had moved to another State.

Four years later, he suffered from mild abdominal pain. His temperature rose to 99° F., and a small mass was said to be discovered in the right iliac fossa. This subsided in two weeks under conservative treatment, and he was again told to return for operation in three months. However, ten days later, he was admitted to another hospital, with the history that he had never felt well since his discharge from hospital. He commenced to have sweats and rigors with vomiting and loss of weight and appetite. No further abdominal pain occurred. Examination disclosed that the patient was very ill and emaciated, his temperature being 104° F. He was jaundiced and his liver was enlarged and tender. No tenderness was present in the right iliac fossa, but palpation revealed a thickening in that region. Bile pigment was present in the urine, and the leucocytes numbered 18,000 per cubic millimetre of blood, 80% being neutrophile cells. His condition rapidly became worse, and he died eight hours later.

Post-mortem examination disclosed a thick-walled retrocaecal abscess containing the remains of a ruptured gangrenous appendix obstructed by a faecolith. The liver was the seat of suppurative portal pyelphlebitis. Culture of the pus from the abscess and the liver yielded a growth of *Bacillus coli communis*.

Case XIII.

A woman, aged sixty years, gave the history that at the age of fifty-five years she had an appendiceal abscess, which was treated by conservative measures. She was for seven weeks in hospital and was well for the next five years save for vague aching and pain in the right iliac fossa. These became accentuated, and a tender swelling was palpated in the right iliac fossa. She refused operative treatment and would not enter hospital. She became anæmic, lost weight and suffered from rigors and sweats. Ten days later she was admitted to hospital, where she was seen to be very ill. Her temperature varied between 99° F. and 104° F., and she was wasted and jaundiced. The liver was diffusely enlarged and tender, and a tender swelling was palpated in the right iliac fossa. Before any further investigation could be undertaken, her condition became poor and she died twelve hours later.

Post-mortem examination revealed a large retrocaecal abscess, which had eroded the ilio-psoas muscle. In it were the remains of a ruptured gangrenous appendix and a large faecolith. The liver was the seat of suppurative portal pyelphlebitis. *Bacillus coli communis* was grown on culture from the abscess and the liver.

Comment.

These last two cases illustrate a rare complication of an appendiceal abscess. Early operation would have prevented these tragic results.

Summary.

The clinical histories of thirteen patients suffering from recurrent appendiceal abscess are presented.

The causes, diagnosis, treatment and results of treatment are discussed.

Of the thirteen patients, two who were unable to receive operative treatment died of suppurative pyelphlebitis.

Acknowledgement.

I wish to thank the Director-General of Medical Services, Australian Military Forces, Major-General S. R. Burston, for his permission to publish this article.

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Reviews.

A YEAR BOOK OF GENERAL THERAPEUTICS.

"THE 1944 YEAR BOOK OF GENERAL THERAPEUTICS", edited by Professor Oscar W. Bethea, is a useful volume.¹ It has three main subdivisions dealing respectively with antipathogen therapy, restoratives and function modifiers. There are two small sections on general therapeutic technique and non-pharmaceutical therapeutics. The sulphonamides and penicillin hold pride of place in the therapeutic field and nearly one hundred pages are devoted to their consideration. The editor points out that sulphadiazine and sulphaguanidine are in their respective spheres the most commonly used. Several references are made to toxic effects of the sulphonamides, and these are worthy of study. The place of sulphamerazine and sulphamethazine in sulphonamide therapy has not yet been determined. No aspect of recent work on penicillin seems to have been omitted. The other subjects considered under the heading of antipathogen therapy include tyrothricin, antiseptics and germicides, burns, antimalarials, antisyphilitics, antirheumatics, antibodies and antigens. In the section on restoration more than thirty pages are given to hormones; endocrinology proper is given a good deal of space in another volume in the series. Transfusions and infusions are dealt with at some length and twenty pages are devoted to vitamins. In the introduction to the vitamin subsection the editor remarks that vitamins have been pushed into a subordinate position by the sulphonamides. He insists on their large field of usefulness, and he regrets their commercial exploitation as well as the fact that practitioners have assisted in it by giving out samples and by telling patients what to get instead of writing prescriptions. Included among the function modifiers are: anaesthetics; sedatives, hypnotics and antispasmodics; drugs acting specially on the autonomic nervous system; drugs acting specially on the heart and blood vessels; anticoagulants; diuretics; thiouracil. Attention is rightly drawn to subclinical cases of barbiturate poisoning—"those that impair and handicap the comfort or well-being of the victim without reaching the degree of severity that secures medical attention".

This is a volume in which every practitioner will find something useful.

Notes on Books, Current Journals and New Appliances.

SERVICE IN NEW GUINEA.

IN "Record of Service", Captain Bruce Robinson, of the Australian Army Medical Corps, has written an unpretentious account of some of his experiences during the New Guinea campaign, in which he served both as a regimental medical officer and on the staff of hospitals.² Captain Robinson has a happy facility for description, whether of places or people; a notable example is his pen picture of the redoubtable Captain Vernon, who at the age of something over seventy years was being determinedly "tough". Tribute is paid to the work of the padres and of the various organizations whose activities in the front line have done so much to lighten the load of the troops. One point that will no doubt interest psychiatrists is the author's statement that, while he was in charge of a regimental aid post in the Sananda area, of the few psychiatric casualties whom he had to treat, only three needed to be evacuated; of these three, one went right back to Moresby, and the other two stayed for a week at the Soputa field ambulance and then rejoined their unit. There is much wholesome information in this little book, which could profitably be digested by all of those who find the New Guinea campaign of secondary interest; the heart-breaking obstacles and conditions of jungle warfare in this area should be more widely appreciated. The book is written primarily for lay readers, but members of the medical profession will find in it much to interest them. It is delightfully illustrated with drawings by the author, and well printed and produced.

¹"The 1944 Year Book of General Therapeutics", by Oscar W. Bethea, Ph.M., M.D., F.A.C.P.; 1944. Chicago: The Year Book Publishers Incorporated. 7" x 4½", pp. 447, with many illustrations. Price: 25s. 6d.

²"Record of Service: An Australian Medical Officer in the New Guinea Campaign", by Bruce Robinson, A.A.M.C., A.I.F.; 1944. Melbourne: Macmillan and Company Limited. 7" x 4½", pp. 183, with 19 illustrations. Price: 6s. 6d.

The Medical Journal of Australia

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All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

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MEDICINE AND THE STATE.

In these latter days discussions on medicine in its relation to the State have been both many and prolonged; their participants have included practitioners in every branch of medicine as well as laymen interested in the public welfare and of every shade of political opinion; and the opinions expressed have been as divergent as might be expected in the circumstances. Intelligent men and women know how difficult it is to rid the mind of prejudice, to view dispassionately a subject with personal implications; and it is not to be wondered at that in discussions on medicine and the State motives are apt to be misunderstood, tempers to be frayed and umbrage taken where no hurt or slight is intended. The proper way in which an attempt should be made to view a subject is to view it whole, for then only can it be seen in relation to other matters or entities. Doctors are accustomed, as we all know, to refer to the tradition of medicine. They believe that certain principles, certain usages, have been handed down through the centuries and that these may be used as an ensample of present-day conduct. At the same time they know that medicine can never be stationary, either in the content of knowledge on which it is based or on the ways in which that knowledge may be applied to the prevention and alleviation of human suffering. This means that doctors regard medicine in the light of history and as still in the process of evolution. What is true of medicine is true also of society, the whole community which comprises the State. To obtain a correct, a balanced, view of society we must see it in the light of history, we must recognize from what it has evolved and that its evolution is not complete. When society, the community, as a single body, acts as law-giver or as guardian of the rights and general well-being of the people, it becomes the State. Among

those who discuss the relationship of medicine and the State will always be found some who are blind to the evolution that is going on in one or the other. There is no doubt that clarity of vision in this matter facilitates the making of decisions that have to be made and helps in the understanding of views advanced by those who appear to err on the side either of conservatism or of drastic change. With these considerations in mind it will be useful to consider an address recently given to the Middlesex Hospital Medical Society by Lord Horder, who is consulting physician to Saint Bartholomew's Hospital, London.¹

At the outset of his address Lord Horder stated that there were three elements in the situation that was being discussed by the Government and the medical profession in Great Britain. These were medicine, society and the State. He then set out to define the roles of all three. Likening the situation to a drama, he said that the play would be a good one in proportion as the two principal actors, their proper roles being assessed, followed their cues. In regard to medicine he remarked that a definition was impossible, and that even a description was a bold thing to attempt. Making the attempt, he described medicine as "a great corpus of knowledge and technique, a tradition, a steady stream of advance in science and art applied to human welfare, a brotherhood of common interest among those inside, and a great fund of goodwill towards those without". No description of medicine will be accepted as satisfactory by everyone. Though the idea may be implicit in the words "applied to human welfare", it would probably have made for completeness if in the present state of affairs some reference had been made to the meeting of human needs that arise as a result of the evolutionary changes taking place in society. However, Lord Horder continued his description by the statement that the material upon which medicine lives and out of which it grows is "all created things". Though this is so, the special study and care of medicine are the body and the mind of man. To this he added the large body of men and women all over the globe who are the disciples of medicine and in whom, "more than in books and museums and laboratories and even hospitals", the spirit of medicine is resident. After being at some pains to show that devotion to medicine leaves its mark upon the doctor's character and even upon his face, Lord Horder stated three axioms. His first is that medicine is resident in a personnel and that to take away the personal element from medicine is to emasculate it. He holds that if the doctor is controlled by more than the control accepted by every member of the community, if he is stereotyped and deprived of his individuality, a great disservice is done to medicine and therefore to society. His second axiom is that a man does better work for himself and his security than he does for the State. What this means is not quite clear. If it means that a man would rather be his own master than be controlled by someone else, we shall agree. From the context, however, Lord Horder appears to think that the service motive is a pretence and that the profit motive and self-interest are all-important. If this is to apply to medical practitioners, not everyone will agree that no good work is done unless a large income is earned. The third axiom is that science, in order to progress, demands

¹ The Lancet, March 10, 1945.

absolute freedom from political control, and that since the best part of medicine is a by-product of science, the same freedom must exist for medicine also. About the acceptance of this "axiom" there can be no question. Lord Horder quoted with approval Herbert Spencer, who declared that vigilance was needed far less against foreign aggression than against "the insidious growth of domestic interference with liberty".

So much for Lord Horder's views on medicine. Turning to his views on society and the State, we note with approval his assertion that neither medicine nor the State can make a man healthy, in a "positive" or any other sense, unless he wills it. He refers to a memorandum issued by the Medical Women's Federation which states the view that "doctors, while having an obligation to society for the treatment of individual patients, have also a duty to interest and educate public opinion in medico-social questions so that these may be approached with understanding and sympathy". To this he fully subscribes. He quotes six other matters in the memorandum in regard to which the doctor is to help, namely, (a) a lowering of the standards of honesty and of consideration for others; (b) an increase in delinquency, involving juvenile delinquency; (c) a more widespread and growing habit of indulgence in alcohol among young people; (d) the loosening of family ties; (e) sexual continence; (f) the toleration of a low standard of certain types of reading matter and of public entertainment. He asks himself whether members of the medical profession really do society a good turn by carrying not only the baby but the whole family on their shoulders. He points out that the profession has quite an extensive and legitimate sphere in helping to keep the fit, fit; in making those near to fit quite fit; and in restoring if possible those who fall by the wayside. The trouble, of course, is that it is not always possible to set a limit on the duties of a practitioner of medicine. To keep a fit person fit or to make fit one who is near fit, any and every aspect of the patient's life must be tackled. Again, experience in this country suggests that when responsible medical practitioners take a leading interest in organizations which deal with sociological rather than with purely medical questions, they are likely to meet with success. The activities of the Returned Medical Officers Association in Queensland in regard to alcohol may be quoted in this regard. The State has duties and responsibilities, but the State is made up of persons grouped together as a community. Each member of the community has responsibilities according as he has knowledge and gifts, and he must find opportunities to use them. When Lord Horder contends that the first and foremost part which the State has to play in the matter of health is a protective one, it must not be presumed that he would take from the practitioner his part in preventive medicine. He sets out at some length what he regards as the protective function of the State and avers that the impact of it all on the nation's health is definite. He would substitute "medicine" for "health" in Virchow's dictum, which would then be: "Politics is nothing else than medicine on a large scale." He concludes that it is right that medicine should infiltrate politics, but that it is disastrous for politics to attempt to infiltrate medicine. Medical practitioners will all know exactly what Lord Horder means by the infiltration of politics into medicine. The statement brings us back to our original thesis that

medicine is not and cannot be static, that an evolutionary process is also taking place in society and that medicine must try to meet the needs of society as it develops while at the same time it is true to its own tradition of service and freedom of action. Apart from the question of the general medical service of the community and the bringing about of changes and reforms in medical practice declared by the profession itself to be necessary, there are other avenues in which energetic action is needed. Industrial medicine, child welfare and obstetric practice are some of the matters about which the profession through its own association should not cease to clamour for action. To be alive is good; to lead a lively existence is better. The one is a gift from the gods; the other owes something to personal effort.

Current Comment.

BLOOD VESSEL ANASTOMOSIS BY A NON-SUTURE METHOD.

Not much imagination is needed to appreciate the far-reaching results that would be possible if the continuity of blood vessels could be restored with anything like the ease with which it can be destroyed. In war surgery particularly, the main vessels supplying the limbs are so often injured that amputation has to be performed. This has been one of the main incentives to experimental work on the blood vessels of animals. Some remarkable results have been achieved, not only in traumatic surgery, but also in other clinical conditions. It would appear from the latest reports that medicine is on the threshold of important advances in vascular surgery. Progress may be traced from the early years in this century. In 1908 Alexis Carrel published an important paper on the results of the transplantation of blood vessels, organs and limbs.¹ He pointed out that vascular surgery had reached an active stage of development with the experiments of Murphy in Chicago and Payr in Graz. Murphy united arteries by invagination and suture, while Payr used a magnesium tube. Hoepfner, in 1903, reported results obtained by the use of Payr's method. The results recorded by Carrel included the transplantation of segments of arteries and of veins. He used fresh vessels and also vessels which had been preserved in cold storage. By means of end-to-end circular suture he obtained good results even when the vessels were of different calibre. He pointed out that the transplantation of arteries was easier than the transplantation of veins, and declared that if veins could act as a substitute for arteries, the problem of the treatment of large wounds or of resection of arteries would be solved. He found that thrombosis occurred more frequently with veins used as transplants than with arteries, and thought that this might be due to the difference of calibre of the vessels used. He found that the approximation of the intimas was difficult, and also that fibrin became deposited on the foldings of the vein and might produce obliteration of the vessel. At the same time he found that a segment of vein transplanted into an artery immediately underwent considerable change. Its lumen was dilated, but its walls became thicker and stronger. No aneurysm occurred. In other words, the vein adapted itself to its arterial functions and reacted against the increased blood pressure by thickening its walls. He thought that on the whole the transplantation of veins on arteries was less safe than the transplantation of arteries on arteries.

The next development occurred after the discovery of heparin by Howell in 1916. The demonstration of this

¹ *The Journal of the American Medical Association*, Volume LI, 1908, page 1662.

natural anticoagulant of the blood raised hopes that it might prove valuable in the clinical prevention of thrombosis. In 1938 G. D. W. Murray and C. H. Best reported some experimental work¹ from which they drew the tentative conclusion that heparin in its purified form was non-toxic both experimentally and in human beings, and that in lesions where intravascular clotting was a problem it might be useful. In 1940 Murray, writing on the use of heparin in the surgical treatment of blood vessels,² reported *inter alia* that he had used heparin with success in the application of a venous graft to an artery in a case of popliteal aneurysm. At this stage, A. H. Blakemore, J. W. Lord, junior, and P. L. Stefkó introduced what they described as a non-suture method of bridging arterial defects.³ Their experimental work was done on dogs and they used a tube of vitallium. Vitallium is a substance of the following composition: cobalt, 65%; chromium, 30%; molybdenum, 5%. The vitallium tube was lined by a segment of vein, the ends of the segment being reflected like a cuff at each end of the tube. The vein-covered ends of the tube were then inserted into the cut ends of the artery whose continuity had to be restored and were held in place with ligatures. Sometimes Blakemore, Lord and Stefkó used two small vitallium tubes, and in these circumstances a segment of vein unsupported by a tube formed the link. It should be noted that the lumen of the reconstituted vessel is completely lined by *tunica intima*.

Blakemore and Lord have now published a further experimental and clinical study of their method.⁴ The contribution is well illustrated and one figure in particular makes the technical details of the procedure quite clear. They have brought their technique to such a stage of perfection that with careful attention to detail of asepsis and the use of a generous segment of vein, they can achieve success in bridging defects of the small femoral arteries of dogs in 90% of cases without the use of anticoagulants. The method has been used to anastomose the abdominal aortas of dogs. Three animals were observed for a period of eight months, and on exploration the anastomoses were patent and the vein grafts were not dilated. A series of studies was carried out in which five sets of animals were used and ten or twenty anastomoses were made in each series. Sulphanilamide was placed in alternate wounds throughout. Sulphathiazole was given by mouth twice a day to dogs in two series, one of which was treated by the Carrel suture method and one by the non-suture method. Irrigation of the wounds with saline solution was carried out in one Carrel suture series and in one non-suture series; and in the remaining three series careful *débridement* of the wounds was carried out when the anastomoses were made. It was found that the Carrel suture technique which gave a 10% success rate, was boosted to 40% success by the performance of *débridement* and the use of sulphonamides. With the non-suture method results were much better when anastomosis was carried out in a contaminated wound within six hours of its infliction than when a delay of twenty-four hours was allowed to occur. In regard to *débridement*, in thirteen cases in which anastomosis was carried out and sulphanilamide was applied locally without *débridement*, there were no successes. With *débridement* alone success was achieved in 30% of cases. When sulphathiazole was given by mouth in addition the success rate was 60%; a rate of 85% was achieved when the application of sulphanilamide to the wounds was also used. In all Blakemore and Lord's experimental delayed anastomoses in contaminated wounds hæmorrhage occurred only once. With their non-suture method they have never observed an aneurysm, either at the artery-vein junction or in the vein graft, and they point out that a considerable disproportion in size between graft and artery does not complicate matters.

Blakemore and Lord have also investigated the usefulness of heteroplastic vein grafts and means of preserving

them. (By a heteroplastic graft they mean a graft transplanted from one subject to another.) They have satisfied themselves beyond doubt that if an anastomosed main artery can be kept patent in a soldier beyond the period of post-traumatic œdema up to fourteen days, the extremity will be saved. By that time collateral vessels will have developed sufficiently to avoid the occurrence of gangrene. They record in detail the histories of two patients in whose treatment the non-suture method of blood vessel anastomosis was applied. In each instance a main artery was damaged. One patient was a boy, aged seven years, and the other a boy, aged fifteen years. Considerations of space make it impossible to reproduce the details of their routine treatment in a case of arterial damage. It should be pointed out, however, that before the conclusion of the procedure, twenty to thirty cubic centimetres of saline solution to which ten milligrammes of heparin have been added and 50,000 units of penicillin are injected into the distal artery stump. Blakemore and Lord also give details of a case in which the method was used to restore blood flow in the artery after excision of an arterial-venous fistula, and of a case in which the method was used after excision of a peripheral arterial aneurysm.

So much for the application of this work to wounds. There is no doubt that the method is effective and will be the means of saving many limbs and lives. Blakemore and Lord, however, have carried their work further and have used their method in a way that will have a strong appeal to the imagination. They have established what they call a portal-caval anastomosis for the relief of portal hypertension. They point out that a common cause of portal hypertension is obstruction to the flow of portal blood through the liver caused by Laennec's portal cirrhosis, and that cases of congestive splenomegaly (Banti's syndrome) in which the obstruction may be in the portal or splenic veins, afford a significant group. They explain that in cirrhosis bleeding may theoretically occur from any point in the gastro-intestinal tract. It occurs most commonly from œsophageal varices. Their first experiment was carried out on dogs. The spleen and left kidney were removed. The end of the splenic vein was everted over the end of a vitallium tube and introduced into the end of the left renal vein. So far they have established "portal-caval shunts" in five cases of portal hypertension. In these they have used the single vitallium tube technique. They report three of these cases—the remaining two are too recent to have any follow-up significance. The first patient was a girl, aged five years, who was in *extremis* on account of bleeding from œsophageal varices. The anastomosis was effected after all other methods of treatment had failed. Seventeen months after operation the child is active and goes to school. The second patient was a girl, aged fifteen years, who suffered from repeated massive hæmorrhages into the gastro-intestinal tract. She has had no recurrence of bleeding and is well five months after operation. The third patient was a man, aged thirty-eight years, who suffered from portal hypertension due to cirrhosis of the liver. Five months after operation the patient is well and has no ascites.

The establishment of a portal-caval anastomosis as described by Blakemore and Lord is an heroic procedure, but it is intended to be used in desperate conditions. They admit that sufficient patients have not been operated on and that sufficient time has not elapsed since operation for the efficacy of the procedure to be determined. Their claim that it warrants further trial will be granted. Biochemical investigations carried out at regular intervals after the establishment of this anastomosis would in all probability yield useful information. Blakemore and Lord not unnaturally think of other possible uses for this method and mention the following: (i) Restoration of blood flow by vein graft bridging of arterial defect following the radical excision of neoplasms. (ii) The establishment of a shunt for the alleviation of congenital pulmonary stenosis. (iii) In coarctation of the aorta when complicated by bacterial infection resistant to chemotherapy or in cases in which there have occurred non-fatal episodes attributable to cerebral hypertension.

¹ *Annals of Surgery*, Volume CVIII, 1938, page 163.

² *Archives of Surgery*, Volume XL, 1940, page 307.

³ *Surgery*, Volume XII, 1942, page 488.

⁴ *The Journal of the American Medical Association*, March 24 and 31, 1945.

Abstracts from Medical Literature.

SURGERY.

Treatment of Indolent Wounds by a Growth-Promoting Substance.

A. B. KERR AND H. WERNER (*The British Journal of Surgery*, October, 1944) discuss the treatment of indolent wounds by a growth-promoting substance, "H.E.P.", and report its use in thirty-six cases. "H.E.P." stands for heart extract powder, which was prepared in the following way. Sheep heart muscle was minced and extracted with saline solution in a refrigerator. Alcohol, 96%, was then added and the deposit obtained after centrifugation was dried *in vacuo* over calcium chloride. The deposit was reextracted with ether, and was ready for use after being ground into powder form. It was found that the growth-promoting properties were retained indefinitely, while the dry powder did not tend to become bacterially contaminated. The authors, in view of the difficulty of controlling a clinical investigation into the healing of indolent wounds, resolved to confine the use of the extract to lesions which had failed to heal despite intensive prolonged treatment by orthodox methods and under specialist supervision. During this orthodox treatment attention had been paid to the patients' general condition, and all subjects had received a diet with a high protein and vitamin content. Any obvious local cause for non-healing, such as foreign bodies, had been removed before the period of orthodox treatment was considered to have failed. "H.E.P." was lightly sprinkled onto the wounds after they had been cleansed with normal saline solution, and the wound was covered with gauze soaked in saline solution or impregnated with "Vaseline". No alteration was made in the general treatment of patients. A total of 36 patients with wounds fulfilling the criteria of intractability was treated. Of these cases, thirty-three were regarded as having fulfilled the criteria of success. In three cases there was partial or no response. Within a week of the commencement of treatment the development of fresh pink granulations was usually observed in the base of wounds. This was accompanied or closely followed by epithelial spread from the margins. Thereafter healing proceeded normally and the ultimate scars presented no unusual features.

Repair of Nerve Injury.

L. DAVIS, G. PERRET, F. HILLER AND W. CARROLL (*Surgery, Gynecology and Obstetrics*, January, 1945) have carried out exhaustive studies of the recovery of function following section of peripheral nerves and repair by end-to-end suture and nerve grafts. Four hundred and seventy animals were used and the nerve was the sciatic. Procedures were standardized and identical methods were used in clinical examination. Swelling is always present at the suture lines after end-to-end suture as well as after the application of autogenous and homogenous grafts. The distal suture line of a graft is always larger than the proximal suture line and is larger in a homogenous than in

an autogenous graft. It is the result of the proliferation which unites the severed ends of the graft to the nerve segments. This precedes and complicates, but does not interfere with the regeneration of nerve fibres. Trauma produced by handling and repairing the nerve causes a reactive proliferation. A traumatic zone is present for a short distance from the suture line in both directions and is characterized by necrotic degeneration of the myelin and axis cylinders. In this area the regenerating nerve fibres take a deviating course. In contusion, such as from gunshot injury with or without interruption of continuity, the zone of trauma extends further and is characterized by necrobiosis; the pattern of regeneration is more confused owing to a slower rate of recovery. Regenerating nerve fibres follow the path of proliferating histiocytes in whatever tissue of reaction may form in the gap. The formation of well-developed axis cylinders and of myelin sheaths is observed in the distal segment of the nerve forty-five days after end-to-end suture, although large amounts of degenerative tissue are present. Regenerating nerve fibres enter the suture line during the first seven days after suture. Despite the large amount of regenerating nerve fibres lost, the distal segment always shows a satisfactory neuronization. Muscular atrophy occurs, but recovers faster in end-to-end suture. Motor function returns earlier in end-to-end suture. Sensory recovery appears sixty days after end-to-end suture and ninety days after autogenous grafting; even after one hundred and fifty days no sensory recovery could be detected to pain in cases of homogenous graft. Contractures are seen more frequently after homogenous grafting than after end-to-end suture or autogenous grafting. Trophic ulcers appeared in 3% after suture, in 6% after autogenous grafting, and in 12% after repair by homogenous graft. Reflexes are a very late sign of recovery and are rarely seen even after thirty months. Response to direct electrical stimulation is the most constant and earliest objective sign of recovery and was obtained forty-five days after end-to-end suture. The added trauma in gunshot wounds delays recovery of function, as shown by electrical stimulation. The authors consider that the operation of choice is end-to-end suture, failing that, autogenous grafting, but that homogenous grafting is justified if the other two methods are not available.

Localization of Foreign Bodies.

J. F. BRAILS福德 (*The Lancet*, December 9, 1944) criticizes methods in use for the X-ray localization of foreign bodies and their subsequent removal by surgical procedures. The mere presence of a foreign body is not an indication for removal; each case must be decided on its merits. The radiologist should aim at such accuracy in localization that the operation will take minutes only instead of the lengthy periods sometimes witnessed. A bubble of gas which remains constant or increases in size is a sound indication of infection. The author holds that when a surgeon is convinced that a foreign body warrants removal he should consult with the radiologist as to the best position for the patient on the operating

table; the X-ray examinations are then made with the patient in that position. Metal markers of wire bent in the form of three sides of a square, with the fourth side bent in to form a diagonal, are placed over the approximate site of the body to be removed. Two exposures are made, one vertical and one horizontal, great care being taken not to move the patient, and to centre the central ray over the marker. The skiagrams show the relative positions of the foreign body, the markers and the bony element. If the findings are not accurate enough the markers may be moved and fresh exposures taken. A scratch over the centre of the foreign body may be made with a scalpel. To remove the foreign body the patient is placed in exactly the same position upon the operating table. If the operation is not immediately successful, the author suggests placing artery forceps clipped onto the tissue at the site shown and then returning the patient to the X-ray room for additional exposures, rather than to operate during screening examinations.

Whole Skin Grafts in the Repair of Herniae.

G. B. MAIR (*The British Journal of Surgery*, January, 1945) presents a preliminary report on his experiences with the use of whole skin grafts in the repair of herniae. He states that the Bassini operation, with all its modifications, is not only inefficient, but actually harmful, and should be abandoned. Two alternatives exist, either simple herniotomy combined with repair of the fascia transversalis, or plastic operations involving the use of living fascial transplants. Recurrence rates following these operations are difficult to estimate, but a figure of 12% could be accepted in the case of the Bassini operation. When fascial transplants are used, recurrence is seen in from 3% to 4% of indirect herniae, and in from 7% to 9% of direct herniae, an improvement being seen in spite of the fact that fascial transplants are used in the less favourable cases. There are, however, certain disadvantages in the use of fascia, including the occurrence of post-operative pain in the region of the thigh from which the graft is taken, and the possibility of obvious muscle hernia at this site. In addition, wound sepsis appears to be not uncommon. Also, recurrence may take place between the strands of fascia used in the darning process. There are, too, special dangers associated with the large Gallie's needle which is used for the darning. The author suggests that strengthening of the internal ring and posterior wall of the inguinal canal, and of corresponding deficiencies in other types of hernia, may be performed by the use of whole skin grafts, and he reports his experiences with this method over a period of five years. Skin preparation is performed for three days prior to operation. An ellipse of skin is taken while the incision is being made, the portion removed being about two inches long and one inch at its greatest width. The sac is exposed and excised in the usual way, and the internal ring narrowed and fascia transversalis buttressed by carefully placed sutures in order to give a firm base for the application of the graft. The fat is dissected away from the graft, which is then applied to the posterior wall of the canal. The inner

end is firmly sutured to the lower anterior aspect of the rectus sheath, to the fascia over the *symphysis pubis*, and to the extreme medial edge of Poupart's ligament. The graft is split at its outer end to embrace the spermatic cord. The lower edge is sutured to Poupart's ligament, and the upper edge to the aponeurotic edge of the internal oblique close to the lateral margin of the rectus sheath. It is important that this graft should be sutured in position under tension. Thirty-day chromicized catgut is used. Sulphanilamide powder is insufflated, the external oblique sutured in front of the cord and the skin wound closed. The patient is allowed up on the twentieth day. Certain objections may be advanced against the method. It might be thought that organisms lurking in the hair follicles might cause an undue incidence of sepsis. Proof that this can be disregarded lies in the practical experience of the method. Another suggested objection is the danger of the growth of hair in the graft, and the possibility of epidermoid cyst formation. Both experimental work and practical experience in human cases show that where the graft is sutured under tension, a metaplasia of the tissue occurs, and the whole of the graft is converted into tissue indistinguishable from very vascular normal connective tissue. A series of 88 cases in which this method was used is reported; the majority of the herniæ were inguinal, but umbilical, ventral, femoral and epigastric herniæ are also included. No figures of recurrence rates can be given, as most of the operations are of too recent date, and the author stresses the fact that this is essentially a preliminary report.

Mediastinal Cysts of Enteric Origin.

W. E. LADD AND H. W. SCOTT (*Surgery*, December, 1944) report a series of five children who were found to be suffering from enterogenous cysts of the mediastinum, or as the authors prefer to call the condition, duplications of the oesophagus. The embryology of the condition still appears to be a matter of some conjecture. Pathologically, a cyst is found in the posterior mediastinum, usually in its middle third, expanding into the right or left hemithorax, but remaining retropleural in location. The wall of the cyst contains usually a two-walled muscular coat resembling oesophagus wall, and a lining of mucosa which may have the characteristics of oesophageal mucosa, but may resemble gastric or duodenal mucosa. The contents of the cyst may resemble gastric juice in containing hydrochloric acid and rennin and pepsin. It is not surprising, therefore, that peptic ulceration may occur in the cyst lining, and this may even perforate into the pleural cavity or lung. An important practical point in the pathology is that there is usually a firm attachment to the oesophageal wall with no intervening plane of cleavage, the muscle coats being continuous. There is no record of such a cyst having a fistulous communication with the lumen of the oesophagus. Clinically, the condition occurs in young children, the oldest recorded case being in a boy, three and a half years of age. Common symptoms are those of pulmonary and bronchial compression, such as cough, dyspnoea, cyanosis and recurrent or chronic pneumonia. Dysphagia or

regurgitation of food may occur from oesophageal pressure. Pain may be caused by distension of the cyst. Hæmatemesis or hæmoptysis may be seen due to compression. Peptic ulceration of the lining may cause special clinical pictures. Signs of chronic ill health and malnutrition are usually present. Physical examination alone rarely allows of a specific diagnosis. Plain X-ray pictures and bronchograms and barium "swallows" may be helpful. Occasionally, erosion of the vertebral bodies or ribs may be found by X-ray examination. Treatment is governed by the pathological feature of firm fixation to the oesophageal wall. This usually precludes the possibility of complete excision of the cyst. The technique used by the authors is one of marsupialization of the cyst with subsequent packing of the sinus and possibly the application of sclerosing substances to destroy the lining mucosa. Three of the five reported patients have survived this procedure.

Muscle Herniæ.

H. E. SIMON AND H. A. SACCHET (*The American Journal of Surgery*, January, 1945) report twenty-four muscle herniæ occurring in twelve patients, and suggest that this condition warrants more careful consideration than has been given to it, particularly in view of its frequent recognition in military personnel. Muscle herniæ occur predominantly in males, only one of the 163 cases in the literature being in a female. Some muscle herniæ may be congenital, but the authors were unable to find any reports of cases in which the condition became apparent sufficiently early in life to suggest this. Acquired herniæ are either traumatic or idiopathic or spontaneous. In the twelve patients reported there was a history of direct injury in three, and trauma featured in a similar proportion of the cases reviewed from the literature. Among the causes of trauma were wounds from bullets, axes, hooks, surgical operations and injuries from fractures. In the idiopathic cases the patients usually give a history of strenuous activity in work or sport. The typical complaint is of a swelling associated with slight or moderate aching, and some tendency to fatigue. On examination a soft semifluctuant swelling is found, which will be situated in relation to a previous injury, or will in the idiopathic group most commonly be found over the *tibialis anterior* muscle, just lateral to the middle third of the tibia. The swelling is readily reducible on pressure, and the margins of the fascial defect can be felt. The swelling appears when the muscle involved is relaxed, and disappears when the muscle is contracted or the limb elevated. Differential diagnosis is from the following conditions. In localized varicosity the overlying skin is discoloured and aspiration yields blood. Arterio-venous aneurysm is characterized by thrill and bruit, does not change with muscle contraction or position of limb, and also permits aspiration of blood. Muscle or tendon rupture produces a swelling which disappears on relaxation and becomes prominent on contraction of the muscle. Lipomata cysts *et cetera* are suggested by herniæ where the presence of adhesions interferes with reducibility. Treatment is called for only when symptoms justify operation. The defect

must be completely exposed and then repaired, by simple sutures, by complete fascial graft or by strips of fascia. Undue tension should be avoided, and when reduction cannot, through excessive volume, be readily accomplished, a portion or all of the protruding muscle may be excised.

Skin Grafts.

H. A. ZINTEL (*Annals of Surgery*, January, 1945) describes a method of resplitting ordinary Padgett skin grafts so that an area two to three times that of the donor area may be successfully covered. After the graft from the donor area is cut, it is placed on the drum of a Padgett dermatome and split into thicknesses of 0.008 inch. Care must be exercised that the donor skin is moisture and fat free, and that the cement fixing the graft to the drum has had time to set firmly before it is cut, that is, from five to ten minutes. It has been found possible to split the original graft into three layers. The cosmetic results are stated to be quite satisfactory. After application of the resplit grafts to the denuded area, they are fastened down by means of paraffin gauze, over which suitable dressings are applied.

Steam Pressure Sterilization.

THEODORE E. WADE (*The American Journal of Surgery*, January, 1945) calls attention to some principles of physics and bacteriology involved in sterilization by autoclaves. He maintains that by taking greater advantage of these, the speed and accuracy of sterilization may be increased. An important point is the fact that moist heat achieves the destruction of bacteria and their spores much more rapidly than does dry heat. The author considers first the conditions obtaining in a space entirely occupied by steam. Here the total gas pressure and the water vapour pressure are identical. At a water vapour pressure of 30 pounds per square inch (that is, 15 on gauge plus 15 atmospheric), the temperature cannot be less than 121° C. Any object in this space which has a temperature less than 121° C. will absorb heat from the steam, which rapidly condenses on its surface, until its temperature reaches 121° C. During this process of condensation the pressure in the neighbourhood of the object will be lowered, and consequently fresh steam will flow towards this neighbourhood. If, however, there is a mixture of air and steam present, then, as the steam condenses to water, which trickles away, the object becomes surrounded by a blanket of air which insulates it from further steam. If simple diffusion is to be relied upon, much time must be allowed and considerable uncertainty must exist as to the degree of penetration of the steam. The alternative method is to remove the air forcibly and to replace it by steam, maintaining the latter at a known pressure for a known length of time. This is done by alternately filling the chamber with steam to fifteen pounds' pressure and exhausting to minus fifteen inches of vacuum. This process is repeated four times, only a small fraction (estimated at one sixty-fourth part) of the air originally present being left. The author describes an arrangement permitting this to be done readily, and records the results of various experiments designed to test the efficacy of the method.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on April 26, 1945, at the Robert H. Todd Assembly Hall, British Medical Association House, 135, Macquarie Street, Sydney. Dr. E. A. TIVET, the President, in the chair.

Complications of Sulphonamide Therapy.

DR. R. G. S. HARRIS read a paper entitled "Experiences, Dangers and Sequelæ of Sulphonamide Administration" (see page 653).

DR. E. H. M. STEPHEN read a paper entitled "Experiences, Dangers and Sequelæ of Sulphonamide Administration in Childhood" (see page 655).

MAJOR W. D. STURROCK said that the only two sulphonamides that had caused any bother in the services were sulphathiazole and sulphamerazine, particularly the latter. Sulphanilamide had been absolutely safe, except in cases of extensive burns in which repeated applications to large areas could raise the blood sulphonamide level to astronomic heights. In these cases anuria from tubule deposition of crystals occurred. In sulphamerazine crystal anuria the outstanding lesion was ureteral block and not as far as they could tell block in the renal tubule. He had seen six cases of obstruction of the ureter, two of which were unilateral, and in three of these cases less than twenty grammes had been given.

Danger signals were renal pain and a diminished urinary output. Even though the urinary output might return to normal with treatment, persistent pain required investigation by cystoscopy. The cystoscopic findings had been as follows. In the first place in the most severe cases there was a gross hæmorrhage from the bladder with contraction of that organ. Only one to two ounces could be put in even with pressure; the slightest touch on the mucous membrane by the cystoscope caused hæmorrhage. Both ureters were blocked with crystals which could be seen protruding from the ureteral orifices. There were crystalline plaques on the bladder wall. Secondly, acute hydronephrosis occurred in one case in which bilateral nephrostomy had to be done. The renal pelvis were swollen and tense. The urine from these contained red blood cells, but was not very abnormal. The pelvis were not congested. In treatment copious fluids should be given by mouth and intravenously during administration. Next came the intravenous administration of alkalinized ten molar solution of sodium lactate with 1% solution of sodium bicarbonate. He had not found it necessary to give this oftener than twice in twenty-four hours. Once obstruction had been overcome sodium sulphate in 3.8% solution might be needed to start the kidney secreting. Cystoscopy should be done after this. If there was any doubt about patency of either ureter, or if pain persisted. The bladder was washed out with 1% solution of sodium bicarbonate and the ureters were catheterized. To do this crystal debris had to be washed away gently with the sodium bicarbonate solution.

If the urine recovered from the kidney contained much debris, a catheter should be left in the ureter for twenty-four hours, and the pelvis washed out every three hours gently with three to five cubic centimetres of sodium bicarbonate solution. The failure of catheterization of ureters made nephrostomy imperative; the ureters had then to be catheterized or washed out from above. Once this had been done, no trouble was experienced with nephrostomy leakage.

DR. A. C. TELFER thanked the speakers for their papers; he remarked that at the present time it was an effort for men to do more than their ordinary routine work. Dr. Telfer criticized the form of the meeting. He said that two papers had been presented, both by clinicians. At such meetings one of the speakers should be a physiologist or pathologist, or a research worker from a laboratory. Dr. Telfer thought that one or two questions ought to be asked during the discussion. Dr. Harris had said that three types of renal damage might occur during the administration of sulphonamides, two types affecting the parenchyma and the other affecting the collecting system. They all, as clinicians, recognized the type of damage that affected the collecting system; but Dr. Telfer did not know that any physiologist or pathologist had actually determined what was the damage to the parenchyma. Was it due to sensitivity? Was it due to the toxic action of the drug on the cell? Dr. Telfer did not know what caused the damage. It might be due to

acetylation or conjugation of the sulphonamide in the liver or kidney; it would be interesting to know what actually did take place in those organs. Dr. Telfer thought that as clinicians they did not keep in sufficient touch with the research worker; views should be exchanged between them. Dr. Telfer then referred to the precautions taken at a large military hospital in Sydney to prevent complications of sulphonamide therapy. He wondered whether alkalinization of the urine was the chief form of prevention, and was by no means sure that it was; he thought that the fluid balance should be carefully watched. In fact, he placed an adequate fluid balance first of the two means of prevention of complications, and then alkalinization of the urine. Dr. Telfer thought that alkalinization of the urine was excessive at the military hospital to which he had previously referred. Recently at Sydney Hospital a few experiments had been carried out, to see how quickly urine could be rendered alkaline by the administration of sodium bicarbonate; it had been found that the pH could be made to rise to more than 7.0 within four hours. Therefore, if patients were given five grammes of bicarbonate of soda, the urinary pH would rise from 4.8 to 7.5 in four hours. Dr. Telfer wondered whether that excessive amount of alkalinization was actually necessary. Dr. Telfer said that he had listened with interest to the remarks made by Major Sturrock, and that brought him to another point. More should be heard from the men in the services and from men who had returned from active service, especially in such a subject as that under discussion; they had had far more experience in the treatment of anuria and other complications due to sulphonamides than had civilian practitioners. In that regard also Dr. Telfer did not think that civilians were hearing sufficient of the excellent work being done in the Australian Army Medical Corps. Good articles were published in THE MEDICAL JOURNAL OF AUSTRALIA, but there were not enough of them. Dr. Telfer hoped to see the publication of more service work in their own journal, not only on such subjects as complications of sulphonamide therapy, but also in regard to tropical diseases.

SURGEON CAPTAIN LAMBERT ROGERS, R.N.V.R., said that the criticisms of sulphamerazine made by Major Sturrock had been made in the Philippine and elsewhere in the tropics, because the high temperature enhanced its bad effects. It was looked upon as a rather dangerous member of the sulphonamide group, and a return to the more soluble sulphanilamide had taken place. However, there was a noticeable tendency for less and less of the sulphonamide drugs to be used, and more penicillin employed in place of them. Surgeon Captain Rogers supported the criticism of sulphamerazine that had been made on its use at the military hospital previously mentioned; he said that he had had experience of one case in which the ureters became blocked with crystals, and he had heard of others.

DR. J. W. S. LAIDLEY said that he had been interested to hear both Dr. Harris and Dr. Stephen urge that great caution should be observed in the administration of sulphonamides to patients with poor renal function and to the aged. Dr. Laidley thought that such statements needed qualification; he did not think that any great care was necessary in the administration to elderly men of the ordinary doses of sulphonamides, provided the urinary output was good. Dr. Laidley would be more worried in administering the drug to a person with oliguria due to acute nephritis *et cetera*. He had for some time found that elderly men who were recovering from prostatectomy or some similar procedure tolerated well ordinary doses of sulphonamides, without complications. Dr. Laidley then referred to Dr. Stephen's condemnation of the use of sulphonamides for trivial complaints. Dr. Laidley said that such misuse happened every day, not only among the resident medical staffs of hospitals, but also in the practice of the busy doctor who saw his patient for a short time and was apt to prescribe sulphonamide as the quickest and easiest way out. Dr. Laidley recalled one case, the general outline of which had been quoted by Dr. Harris. The patient, a woman, had had one kidney removed, and at subsequent operation the remaining ureter was accidentally ligated; as a result she immediately became anuric. This condition was within four days relieved by the establishment of a pyelostomy; that meant that she had undergone two major operations within a very short time. Her temperature, as was to be expected, rose to 101° or 102° F. An enthusiastic resident medical officer prescribed sulphathiazole, and in three days the patient was anuric again. Dr. Harris had mentioned another case in which some unfortunate person had been given sulphanilamide on a second occasion, after convincing proof that she could not tolerate it. Dr. Laidley said that unless resident medical officers were closely watched, nine out of ten patients would be given sulphonamides without adequate reason, just because they had a

rise in temperature. A third point was the question that had been asked as to whether alkalinization of the urine or the maintenance of an adequate fluid balance was the more important means of preventing complications of sulphonamide therapy. Dr. Laidley said that for his own part he felt much happier if the patient's urinary secretion did not fall below fifty ounces per day; in such circumstances the idea of anuria did not cross his mind. Both he and biochemist friends of his held that the amount of urine excreted was the really important thing, and that alkalinization of the urine fulfilled a secondary role.

DR. S. G. BRADFELD thanked the speakers for their papers. He said that one point that arose concerned the treatment of agranulocytosis following sulphonamide therapy. Dr. Bradfield had read that the correct treatment was to continue to administer the sulphonamide. He had had experience of only one case. The patient had arrived at hospital four days after a reaction to the drug had occurred; 44 grammes of sulphathiazole had been given, and the temperature had been normal for two days, after which it had risen to 104° F. and remained there. When the patient was admitted to hospital his leucocytes numbered only 170 per cubic millimetre, and no granular cells were present. He recovered after cessation of sulphathiazole and treatment with "Pentnucleotide". In that case the dosage of a sulphonamide had been continued after the patient had shown a severe reaction to the drug, and this treatment had been of no benefit to the patient. Dr. Bradfield asked whether Dr. Harris or Dr. Stephen could comment on this point. Referring to sulphadiazine, Dr. Bradfield said that recently for about three weeks he had acted as resident medical officer at a hospital in Queensland with two recent graduates, who used sulphonamide drugs on the slightest pretext. Frequently the drugs were used because the patient's temperature was raised, not because a diagnosis had been made. Dr. Bradfield thought that among the patients there were quite a number of febrile reactions to the sulphonamide, and it struck him that the patient's stay in hospital was in many cases prolonged by injudicious use of this form of treatment. In conclusion, Dr. Bradfield said that he supported Dr. Laidley's statement that sulphonamide therapy was being used too frequently in minor illnesses.

DR. COLIN EDWARDS said that he had appreciated the papers; it was a great help to have a summary of what had happened in the past presented for review, and to have attention drawn to things that had escaped notice. One or two points that had not been mentioned were worthy of note. The first was the extraordinary rapidity with which substantial calculi could be formed in the renal pelvis. Dr. Edwards said that he had seen in consultation a man suffering from a periurethral abscess, and suggested *inter alia* the administration of sulphapyridine. He heard no more until six weeks later, when he was called to see the patient again. The patient had a considerable amount of pain in one loin and a diminishing urinary output. An X-ray examination revealed a shadow in the pelvis of one kidney. This was considered to be a sulphapyridine calculus; it was at the time unknown that sulphapyridine calculi were not opaque to X rays. The ureter was catheterized and washed out with sodium bicarbonate solution. A few days later a further X-ray picture was taken, and the appearances seemed normal. The man was given more sulphapyridine as soon as he went home. After four weeks' administration further stones were visible and could not be dissolved. They were removed surgically, and found to contain a certain amount of phosphates. This second lot of stones arrived within four weeks; Dr. Edwards said that it was impossible to be certain that the first stone had disappeared. With regard to urinary tract infections, it was not generally realized that antisepsis in the urine depended more on the concentration of the drug in the urine than on the concentration in the blood stream. Therefore, penicillin and sulphonamides, which circulated in the blood stream and were excreted almost entirely in the urine, were needed only in very small doses in infections of the urinary tract. A large number of the obstructions that occurred followed large doses. There were cases of individual idiosyncrasy in which obstruction occurred after the administration of minute doses. Dr. Edwards said that if it was realized that in urinary tract infection large doses were not necessary, a large number of cases of obstruction would not occur. This fact had not been sufficiently emphasized in the literature. The same observation applied to penicillin. In the few cases that had come under his notice, the administration of three cubic centimetres of penicillin solution per three hours was quite sufficient. Dr. Edwards endorsed the protests that had been made against the administration of sulphonamides merely because the patient had an elevation of temperature.

Such a procedure did not mean that a diagnosis had been made, and the result was that the disease was not being treated. If the resident medical officer could be restrained during his period of hospital training, he would also be restrained when he left hospital. Lecturers should lay stress on the fact that sulphonamides were being used too much.

DR. E. A. TIVEY, from the chair, thanked Dr. Harris and Dr. Stephen for their papers. Dr. Tivey said that he had been terrified to hear in Dr. Harris's paper the awful sequelae that might follow the administration of sulphonamides. Dr. Tivey had had no experience of such unfortunate occurrences, although he had possibly been as reckless as most other practitioners in the use of these drugs. In practice their administration was more or less "by guess and by God". Dr. Tivey wondered whether there was any relation between the blood concentration of sulphonamides and crystal deposition in the urinary tract. No mention had been made by either speaker of the concentration that was apt to produce crystals, or whether the deposition of crystals was particularly due to an idiosyncrasy on the part of the patient. Dr. Tivey agreed with Dr. Teifer's suggestion regarding the advisability of having a physiologist or pathologist to read a paper with a clinician on subjects such as that under discussion. Dr. Harris's paper had dealt with the urologist's point of view and the need for caution in the administration of sulphonamide drugs. Dr. Stephen had as usual produced an instructive and entertaining paper.

Dr. Harris said that he was unable to reply to the question about the concentration of a sulphonamide in the blood stream that might be associated with crystallization in the urinary tract. He had had experience of only a small number of cases, and all the patients had arrived in hospital very ill; there had been no time or facilities for testing the blood concentration of the drug. The remarks of Major Sturrock and Surgeon Captain Rogers on the use of sulphamerazine had been helpful, and would have a restraining influence on its use in civilian practice. From what he had read of it, Dr. Harris thought that the only possible advantage of sulphamerazine was the lessened frequency of dosage required—every twelve hours. However, he could see no advantage if that was the only claim made for the drug. It had many disadvantages. Dr. Teifer and Dr. Laidley had referred to the respective merits of alkalinization of the urine and of the maintenance of a satisfactory fluid balance as measures to prevent complications of sulphonamide administration. Dr. Harris said that from the clinical point of view, there was no question that the taking of alkalis by mouth reduced gastric upset and increased tolerance to the drugs. Whether it produced any actual enhancement of the drugs' inhibitory effect on the infecting organism he could not say. In conclusion, Dr. Harris expressed his thanks to those who had joined in the discussion of the papers.

Dr. Stephen, in reply to the question that had been asked about agranulocytosis, said that he agreed that the sulphonamide drug should be suspended immediately if agranulocytosis was detected. Personally he had not encountered an instance of it. He could give no information about what concentration of the drug in the blood stream must be attained before crystals or calculi were likely to be discovered. Estimations of the concentration of the drug had not been made in all cases, but usually in those cases in which intravenous therapy was being employed.

NOTICE.

THE General Secretary of the Federal Council of the British Medical Association in Australia has announced that the following medical practitioner has been released from full-time duty with His Majesty's Forces and resumed civil practice as from the date mentioned:

DR. R. A. PLAYOUST, 480, Military Road, Mosman, New South Wales (June 1, 1945).

Correspondence.

THE PHARMACEUTICAL BENEFITS ACT.

SIR: In view of the ferocious attacks by British Medical Association leaders on the Federal Government's Pharmaceutical Benefits Bill, I was pleased to note the progressive point of view put forward by Colonel H. M. Fisher and colleagues in a recent issue. Mistakes have been made on

both sides. I feel sure that the majority of members of the British Medical Association, especially those in the services, regard the substance of the bill as a good piece of forward legislation. Inasmuch as it brings modern medical benefits, some now indispensable, to adequate therapy, like penicillin, sulpha drugs, and anything that may be discovered in the future, within reach of the lower income earner, it cannot be disregarded by a profession, each one of whose members has, whether he or she likes it or not, sworn the Hippocratic oath. We are honour bound to bring the best of everything medical, surgical and preventive to bear in raising the standard of health throughout the world to its maximum in the shortest possible time. With this the touchstone, the bill may be regarded as a step, though a small one only, in the right direction. Those who attempt to smash this well-meant attempt to better conditions for the masses of the Australian people are therefore reactionary, either misguided or deliberately so. In the latter category are those who subscribe to the view that socialism is a tiger to be avoided at all costs, come depressions, come wars, most of whom do not even understand what it is, and those who view nationalization of medicine, on whatever excuse, in the same light, as a step towards socialism. I regret very much that the leadership of the British Medical Association in a few individual cases at least has taken upon itself, presumably on behalf of the rank and file, to inaugurate a political campaign against a wartime Government (who have done, if not a perfect, at least a fairly good job), instead of attempting to meet the Minister of Health half-way and straighten out the two points in the bill that seem to be the cause of the trouble. I will not attempt to condone Senator Fraser's apparently dictatorial "take it or leave it" attitude—there is no good reason, in view of the profession's decision, why the formulary should not be made all-inclusive, nor is the position *re* the penalty clause such that difficulties cannot be overcome by mutual agreement and the bill amended accordingly. If the British Medical Association leadership persists in fighting the bill as a whole on political grounds, instead of organizing a more acceptable and workable one, it lays itself open to grave charges of exceeding its mandate.

Consider also that even the much-maligned "communist-controlled trade unions" have done everything in their power to avoid wartime strikes in furtherance of the war effort, which should by rights now be at its peak in this country. The threat to boycott the bill, that is, nothing more or less than to stage a strike which will undoubtedly throw the profession in a poor light with the majority of Australians, is straight-out sabotage.

We boast of our democracy, our moderation, our British characteristic of being able to come to terms. Let us in the interests of progress and human welfare remember this and set the machinery in action, in forward gear.

Yours, etc.,

LEIGH S. WALLMAN.

May 16, 1945.

Sir: Your correspondent, Captain L. S. Wallman, has apparently not read the reports of meetings of the Federal Council held during the past eighteen months which have appeared in various issues of *THE MEDICAL JOURNAL OF AUSTRALIA*, for, if he had done so, he would not have made the mis-statements that he has in his letter of May 16.

Although in all good faith it has stated that in trying to improve the health services to the community the Government has started at the wrong end in providing "free" medicines, the Federal Council, which acts for and on behalf of the Branches of the Association in matters affecting the profession as a whole, has studiously avoided expressing any opinion on the political aspect of the "free" medicine question. Indeed, in its letter to the Minister for Health of March 20, 1945 (*vide THE MEDICAL JOURNAL OF AUSTRALIA*, April 21, 1945, page 411), the Council stated that "it had no desire to deprive the public of the benefits of free medicine which the Government had seen fit to offer them".

The Federal Council has in no way attempted to inaugurate a political campaign against the Government, nor, indeed, has it had the temerity to express an opinion as to whether the Government has done a good or a bad job. The Council is not interested in politics.

It is, however, interested in seeing that the community is provided with an efficient health service, and in the maintenance of professional standards, and will continue to voice its opposition to any scheme, no matter who the sponsors may be, which it regards as not being in the public interest.

"Instead of attempting to meet the Minister of Health half-way", the Council has offered him the fullest cooperation of the profession in the working of the *Pharmaceutical*

Benefits Act provided that the objectionable features of the act are removed. That offer still stands, as the letter to the Minister of March 20, 1945, will show. It remains to be seen whether the Minister will still maintain his "dictatorial 'take it or leave it' attitude".

Finally, in order to assure Captain Wallman that the representatives of the profession are willing to "set the machinery in action, in forward gear", I would refer him to the report of the meeting of the Federal Council, September 25 to 28, 1944, which was published in the issue of *THE MEDICAL JOURNAL OF AUSTRALIA* of October 28, 1944, page 464.

Yours, etc.,

J. G. HUNTER,

General Secretary, Federal Council
of the British Medical Association
in Australia.

135, Macquarie Street,
Sydney,

June 14, 1945.

EXOPHTHALMOS AND GRAVES'S DISEASE.

Sir: The review of recent work on exophthalmos and Graves's disease in the journal of June 2, 1945, is long overdue. The commentator is apparently quite unaware of the valuable paper read at the first meeting of the Ophthalmological Society of Australia in Melbourne in 1939 by Dr. Frank Niall, and published in the first volume of the society's *Transactions*. The paper discusses fully the literature up to that date, clinical findings of cases seen and treated in conjunction with Mr. Frank Morgan at Saint Vincent's Hospital, Melbourne, results obtained after Naffziger's method for decompressing the orbits, as well as describing sections of muscular tissue removed at operation. Because of its publication in a relatively obscure journal, the article has been overlooked, and it is not surprising that your commentator regards the present state of knowledge of the subject as being of recent origin.

My own experience does not agree with the statement that the exophthalmos is usually bilateral. Unilateral cases are by no means uncommon, and may be mistaken for intraorbital tumours. So firmly rooted is the belief that exophthalmos associated with Graves's disease is always bilateral, that frank incredulity is often expressed at such a diagnosis when the condition is unilateral. If in addition there are no obvious signs of thyrotoxicosis, such a suggestion may seem absurd. Nevertheless, in my experience, it has more commonly been the cause of the protrusion of the globe than intraorbital tumour. It is not generally appreciated that it may cause papilloedema and optic atrophy, and that the need for surgical intervention may be urgent. After removal of the orbital roof, the papilloedema subsides, and the central scotoma disappears.

Yours, etc.,

KEVIN O'DAY.

33, Collins Street,
Melbourne, C.I.,
June 7, 1945.

REHABILITATION AS SEEN IN THE ROYAL AUSTRALIAN AIR FORCE.

Sir: The article dealing with certain aspects of rehabilitation as applied to the Royal Australian Air Force written by Squadron Leader Graham Andrew, which appeared in your issue of June 9, 1945, must commend itself to all lay and military members of the profession who have at heart the well-being of the sick and injured members of our forces.

His reference to the value of occupational therapy is particularly sound and timely. There is one point, however, upon which Squadron Leader Andrew appears to have been inaccurately informed, and I wish to clear up any doubt which may exist in the minds of some of his readers as the result of one of his statements. I ask him to believe, however, that this action of mine in no way implies any criticism of any of the actual subject matter of his admirable paper.

Under the heading "Occupational Therapy", Squadron Leader Andrew states: "The larger units have on the staff a graduate of the Australian School of Occupational Therapy. Such a three-year course includes training in physiology, psychology and anatomy and a wide knowledge of the arts and crafts." With the exception of one or two graduates of overseas schools, all trained occupational therapists in this country, including those in the forces, are graduates of the Occupational Therapy Training Centre established in Sydney

some four or five years ago by the New South Wales Branch of the Australian Physiotherapy Association and controlled by this body. There is no such organization as the Australian School of Occupational Therapy.

The course of training at the present time is two years. In addition to the subjects mentioned by Squadron Leader Andrew, students undergo a sound training in psychiatry and receive not only an intensive training in various crafts, but what is even more important, are trained in their therapeutic application.

Yours, etc.,

D. J. GLISSAN,
Chairman, Australian Physiotherapy
Association, New South Wales
Branch.

Sydney,
June 13, 1945.

OVERCROWDING IN AUSTRALIAN UNIVERSITIES.

SIR: In the editorial of the journal of June 2, 1945, you state that "a medical school will before long be set up in Western Australia". For over ten years I have been intensely interested in this project and was the first donor to the "medical school establishment fund". However, I do not share your optimism and know that considerable time will elapse before this project is consummated.

The University of Western Australia is unique in the British Empire in that by the *University of Western Australia Act, 1911*, no lecture fees may be charged. This circumstance, while commendable, has led to considerable loss of revenue and will be the greatest obstacle to the establishment of a faculty of medicine. When you consider what would happen to the Universities of Melbourne and Sydney if their incomes were to be reduced by one-third by the abolition of fees you can realize the position.

Last year, by the will of Miss A. Cummins, proprietress of the Kalgoorlie brewery, a sum exceeding £110,000 was left to the university for a medical school, but cannot be realized for many years because of certain provisions. However, I hope in my lifetime to see in this State a medical school worthy of the great schools in the eastern States.

Yours, etc.,

F. W. SIMPSON.

271, Cambridge Street,
Wembley Park,
Western Australia.
June 13, 1945.

The Royal Australasian College of Physicians.

EXAMINATION FOR MEMBERSHIP.

AN examination for membership of the Royal Australasian College of Physicians will be held in September, 1945.

The written examination will be held in capital cities where candidates are offering and, for the convenience of candidates serving in the forces, at other centres if the necessary arrangements can be made. A clinical examination will be held in Sydney and also in Melbourne if a sufficient number of candidates offers. Only those candidates whose answers in the written examination have attained a standard satisfactory to the Board of Censors will be allowed to proceed to the clinical examination.

Dates of Examination.

Written Examination: Saturday, September 1, 1945.

Clinical Examination in Melbourne (provisional): Friday and Saturday, September 21 and 22, 1945.

Clinical Examination in Sydney: Tuesday and Wednesday, September 25 and 26, 1945.

Applications.

Applications to appear before the Board of Censors should be made in the prescribed form and must be in the hands of the Honorary Secretary of the College not later than Saturday, August 4, 1945. Candidates should signify in which city they desire to take the written examination and whether they wish to take the clinical examination in Sydney or in Melbourne. Application forms are obtainable from the Honorary Secretary, 145, Macquarie Street, Sydney.

Medical Prizes.

THE SHORNEY PRIZE.

THE Shorney Prize, established for the purpose of perpetuating the memory of the late Herbert Frank Shorney, M.D., F.R.C.S., lecturer in ophthalmology in the University of Adelaide from 1926 to 1933, will be offered for the first time in 1946.

The relevant clauses of the statute are as follows:

3. A post-graduate prize, to be called the Shorney Prize, of the value of £100, shall be awarded to the candidate who in the opinion of the examiners has made the most substantial contribution to knowledge in the subjects of ophthalmology or of diseases of the ear, nose and throat.

4. The recipient must be a graduate of an Australian university.

5. The material submitted for the prize may be either a thesis or published work in medical or scientific literature.

6. Each candidate must declare that the work described is his own.

7. The prize shall be offered for competition from time to time as the accumulations of the fund permit.

8. The prize shall be offered at least twelve months before the last day for the receipt of applications.

9. The prize shall not be awarded on any occasion unless in the opinion of the examiners the material submitted is of sufficient merit.

Applications, accompanied by the evidence which the candidates wish to submit in support, must reach the Registrar of the University of Adelaide not later than June 30, 1946.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Numbers 109, 114 and 119, of May 31, June 7 and 14, 1945.

CITIZEN NAVAL FORCES OF THE COMMONWEALTH. *Royal Australian Naval Reserve.*

Termination of Appointments.—The appointments of Stanley Corbett Lowe as Lieutenant (Provisional) and Norman Lennox Speirs as Surgeon Lieutenant are terminated, dated 23rd April, 1945, and 15th April, 1945, respectively.

Appointment.—Ronald Wayland Tiver is appointed Surgeon Lieutenant (D), dated 8th May, 1945.

Termination of Appointment.—The appointment of Norman Heaydon Rutledge as Surgeon Lieutenant is terminated, dated 10th May, 1945.

ROYAL AUSTRALIAN AIR FORCE.

Citizen Air Force: Medical Branch.

The probationary appointment of Flight Lieutenant C. H. Knott (277522) is confirmed with effect from 17th April, 1945.

Temporary Squadron Leader V. R. Meek (261662) is transferred from the Reserve to the Active Force with effect from 9th April, 1945.

Reserve: Medical Branch.

The following officers are transferred from the Active List with effect from the dates indicated: Temporary Wing Commander G. J. B. Baldwin (251657), 19th March, 1945, Temporary Flight Lieutenant F. J. Kenny (254851), 20th March, 1945.

The appointment of Temporary Flight Lieutenant G. P. Ryan (257668) is terminated with effect from 29th March, 1945.—(Ex. Min. No. 142—Approved 13th June, 1945.)

Clement Henry Walsh (267801) is appointed to a commission on probation with the rank of Flight Lieutenant with effect from 26th March, 1945.—(Ex. Min. No. 143—Approved 13th June, 1945.)

CASUALTIES.

ACCORDING to the casualty list received on June 19, 1945, Captain W. G. Holt, A.A.M.C., Kings Cross, New South Wales, who had been previously reported prisoner of war, is now reported "recovered".

Honours.

BIRTHDAY HONOURS.

HIS MAJESTY THE KING has been pleased to confer the honour of knighthood on Dr. Sidney Valentine Sewell, of Melbourne. On behalf of the medical profession we offer Sir Sidney Sewell warm congratulations.

Medical Appointments.

Dr. Henry Kenneth Fry has been appointed an official visitor to the Parkside Mental Hospital, South Australia.

Dr. James Davidson Mill and Dr. Henry Edwin Fellow have been appointed honorary clinical assistants at the Sterility Clinic, Royal Adelaide Hospital.

Dr. Nigel Drury Gresley Abbott, Dr. Francis Callum Archibald, Dr. Max Sylvester Cooling and Dr. John Stark Skipper have been appointed resident medical officers at the Royal Adelaide Hospital.

Dr. Douglas Lewis Barlow has been appointed honorary allergist to the allergy clinic, Royal Adelaide Hospital.

Dr. Geoffrey Ernest Peters has been appointed temporary honorary assistant to the surgical section, Royal Adelaide Hospital.

Dr. Abraham Fryberg, Acting Deputy Director-General of Health and Medical Services, has been appointed Deputy Chairman of the Queensland Health Education Council, in pursuance of the provisions of *The Health Acts, 1937 to 1945*, of Queensland.

Australian Medical Board Proceedings.

NEW SOUTH WALES.

THE undermentioned have been registered, pursuant to the provisions of the *Medical Practitioners Act, 1938-1939*, of New South Wales, as duly qualified medical practitioners:

Finlayson, Jean Stanley, M.B., B.S., 1939 (Univ. Melbourne), c.o. Hotel Arcadia, Sydney.

Perec, Charles, L.R.C.P., L.R.C.S. (Edinburgh), L.R.F.P.S. (Glasgow), 1939, 2/9 A.G.H., A.I.F.

Martin, Joan, M.R.C.S. (England), L.R.C.P. (London), 1942, M.B., B.S., 1944 (Univ. London), 9, Springfield Avenue, Potts Point.

Penington, Alan Harry, M.B., B.S., 1933, M.D., 1937 (Univ. Melbourne), c.o. Commonwealth Bank, Pitt Street, Sydney.

The following change of name has been registered:

O'Reilly, Margaret Linnell, M.B., B.S., 1939 (Univ. Sydney), 159, Kent Road, Woolloowin, N.3, Queensland; name now Cleghorn, Margaret Linnell.

The following additional qualification has been registered:

Parker, Keith Shelley (M.B., Ch.M., 1915, Univ. Sydney, F.R.C.S., Edinburgh, 1919), F.R.A.C.S., 1932.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Coyle, Edward Frank, M.B., 1942 (Univ. Sydney), Captain E. F. Coyle, R.M.O., 16 A.I.T.B., Greta.

Short, Leslie Frederick, provisional registration, 1945 (Univ. Sydney), Wollongong District Hospital, Wollongong.

Robey, Ariel Lesley, provisional registration, 1945 (Univ. Sydney), Parramatta District Hospital, Parramatta.

Truscott, Maxwell Steven, M.B., B.S., 1939 (Univ. Sydney), 42, Towns Road, Rose Bay.

Books Received.

"Duodenal and Jejunal Peptic Ulcer: Technic of Resection", by Rudolf Nissen, M.D., with a Foreword by Owen H. Wangenstein, M.D., Ph.D.; 1945. New York: Grune and Stratton. 8½" x 5½", pp. 144, with 123 illustrations. Price: \$4.75.

Diary for the Month.

- JULY 3.—New South Wales Branch, B.M.A.: Council Quarterly Meeting.
 JULY 4.—Western Australian Branch, B.M.A.: Council Meeting.
 JULY 4.—Victorian Branch, B.M.A.: Branch Meeting.
 JULY 5.—South Australian Branch, B.M.A.: Council Meeting.
 JULY 6.—Queensland Branch, B.M.A.: Branch Meeting.
 JULY 10.—Tasmanian Branch, B.M.A.: Ordinary Meeting.
 JULY 10.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
 JULY 10.—New South Wales Branch, B.M.A.: Organization and Science Committee.
 JULY 13.—Queensland Branch, B.M.A.: Council Meeting.
 JULY 16.—Victorian Branch, B.M.A.: Hospital Subcommittee.
 JULY 16.—Victorian Branch, B.M.A.: Finance, House and Library Subcommittee.
 JULY 17.—Victorian Branch, B.M.A.: Organization Subcommittee.
 JULY 17.—New South Wales Branch, B.M.A.: Medical Politics Committee.
 JULY 18.—Western Australian Branch, B.M.A.: General Meeting.
 JULY 19.—South Australian Branch, B.M.A.: Council Meeting.
 JULY 19.—Victorian Branch, B.M.A.: Executive Meeting.
 JULY 19.—New South Wales Branch, B.M.A.: Clinical Meeting.
 JULY 24.—New South Wales Branch, B.M.A.: Ethics Committee.
 JULY 25.—Victorian Branch, B.M.A.: Council Meeting.
 JULY 26.—South Australian Branch, B.M.A.: Scientific Meeting.
 JULY 26.—New South Wales Branch, B.M.A.: Branch Meeting.
 JULY 27.—Queensland Branch, B.M.A.: Council Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phoenix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract practice appointments in Western Australia. All Public Health Department appointments.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such a notification is received within one month.

SUBSCRIPTION RATES—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in the Commonwealth can become subscribers to the journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rates are £2 for Australia and £2 5s. abroad per annum payable in advance.

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THE MEDICAL JOURNAL OF AUSTRALIA



VOL. I.—32ND YEAR.

SYDNEY, SATURDAY, JUNE 30, 1945.

No. 26.

COMMONWEALTH OF AUSTRALIA. DEPARTMENT OF HEALTH.

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The Medical Profession is notified that the Control of Penicillin Order, promulgated in the *Commonwealth of Australia Gazette*, No. 85, of 3rd May, 1944, has been revoked.

The Penicillin Order published in *Gazette* No. 189 of 20th September, 1944, and in *THE MEDICAL JOURNAL OF AUSTRALIA* of 30th September, 1944, relaxes the conditions under which Penicillin may be supplied for the treatment of members of the civilian population.

To obtain Penicillin a Medical Practitioner must apply in the form of certificate set out in the order to the Senior Commonwealth Medical Officer in the State concerned. The signature of a colleague is no longer required.

The addresses of the Senior Commonwealth Medical Officers are: **NEW SOUTH WALES**, Customs House, Circular Quay, Sydney; **VICTORIA**, A.C.A. Building, 118 Queen Street, Melbourne; **SOUTH AUSTRALIA**, C.M.L. Building, 41-47 King William Street, Adelaide; **WESTERN AUSTRALIA**, 4th Floor, G.P.O., Perth; **TASMANIA**, Commonwealth Health Laboratory, Launceston; **QUEENSLAND**, Anzac Square, Adelaide Street, Brisbane.

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Further information obtainable from the General Secretary,

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THE RACHEL FORSTER HOSPITAL FOR WOMEN AND CHILDREN, PITT STREET, REDFERN.—Applications are invited from duly qualified medical practitioners for the positions of: (1) Honorary Physician, (2) Honorary Assistant Surgeon, (3) Honorary Relieving Assistant Gynecologist. Applications on the prescribed form, obtainable from the hospital, together with testimonials, to be in the hands of the undersigned not later than Saturday, 7th July, 1945.—MARY C. PUCKRY, Chief Executive Officer and Medical Superintendent.

THE ROYAL NORTH SHORE HOSPITAL OF SYDNEY.—Applications are invited and will be received up till noon on Saturday, 7th July, 1945, from medical practitioners qualified to fill the undermentioned temporary positions on the honorary medical staff of the hospital: Clinical Assistants for Medicine (2), Clinical Assistant for Medicine (Diabetic Clinic) (1). Applicants should state age, qualifications and experience in these specialities and send copies only of testimonials. By order.—J. H. WARD, Secretary, St. Leonards.

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PUBLIC SERVICE OF SOUTH AUSTRALIA.—Applications from qualified medical practitioners will be received by the Public Service Commissioner, Adelaide, until and including Saturday, 7th July, 1945, for the following positions in the South Australian Hospitals Department: 1. Assistant Medical Superintendent, Royal Adelaide Hospital (bed capacity 800). Term of appointment: one year, with eligibility for reappointment. Salary: £650 per annum, with a living-out allowance of £56 per annum. Duties: responsible to Medical Superintendent for the supervision of the surgical department of the hospital. 2. Deputy Superintendent, Northfield Mental Hospital. Term of appointment: permanent position with superannuation rights. Salary: £847 per annum, from which is deducted a rental charge of £104 per annum. Duties in accordance with Mental Defectives Act. Position also includes relieving duties at Enfield Receiving House when the Deputy Superintendent of that institution is off duty. Must live in residence provided at the hospital; must provide suitable transport between Northfield and Enfield (four miles). Mileage allowance paid. 3. Clinical Pathologist, Royal Adelaide Hospital. Term of appointment: 12 months, with eligibility for reappointment. Salary: £350 per annum (with one meal supplied when on duty). Duties include pathological and bacteriological investigations as required, supervision and instruction of the nursing staff in the collection of specimens in the wards and operating theatres; to instruct and demonstrate in clinical pathology to students. Responsible for post-mortem examinations in the absence of other officers. 4. Registrar, Royal Adelaide Hospital. Term of appointment: 12 months, with eligibility for reappointment. Salary: £225 per annum, with a bonus at the rate of £75 per annum on completion of term of satisfactory service. Applicants must state full names, age, particulars of military service, professional training and experience.—C. A. POUNSETT, Acting Secretary, Public Service Commissioner.

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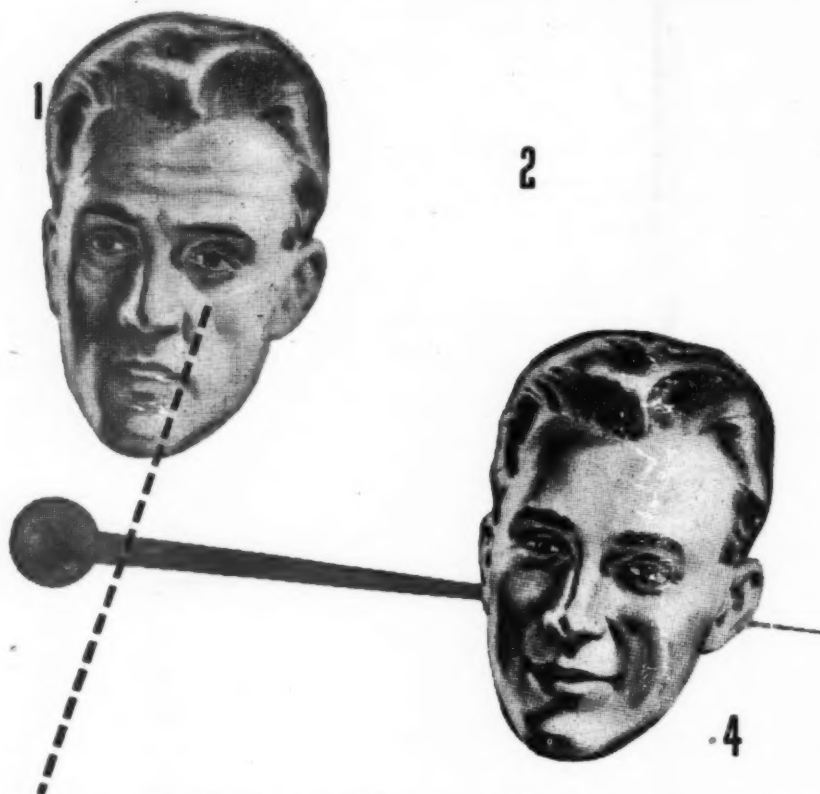
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